The Journal of Pediatrics

VOL. 48 JUNE, 1956 No. 6

BARBITURATE POISONING

[Editor's Note: Some months ago Dr. John K. Wilson, of Greensboro, North Carolina, discussed with two members of the Editorial Board of the JOURNAL (L. F. H. and W. E. N.) an emergency problem with which he had been faced. He was asked to present the problem in the form of a case report. This was referred by the Editor to Dr. Etteldorf with a request for editorial discussion. The editorial prepared by Dr. Etteldorf and Dr. Robert A. Woodbury, professor of pharmacology at the University of Tennessee, was so complete that the Editor decided to follow Dr. Wilson's report with the discussion rather than use it, as originally intended, in "Editor's Column." As the incidence of barbiturate poisoning has been increasing, it was thought that the discussion would not only be of interest, but of service to anyone faced with the situation in which Dr. Wilson found himself.]

ACUTE BARBITURATE POISONING—HOW SHOULD IT BE TREATED?

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ON JUNE 12, 1955, a 4-year-old child was brought to our local hospital comatose from a very large dose of barbiturate. He died fifteen hours later, and I would like to present the sequence of events that occurred during these fifteen hours and ask the question, "Should analeptic drugs be used in acute barbiturate poisoning?" This question I repeatedly asked myself during these fifteen hours.

I will present this in a different manner from the usual case history to illustrate the confusion that exists in the physician's mind when he is suddenly faced with a desperate situation like this one.

At about 8:00 P.M. on June 12, 1955, I received a telephone call from a pediatrician in a neighboring town, stating that he had a 4-year-old boy who had taken an unknown amount of Ipral sodium elixir.* It was estimated that between 15 and 30 grains had been ingested. The child had been found unconscious at about 9:00 A.M. on Saturday, June 11. Respirations had ceased about twelve hours later, and respirations had been main-

*Squibb's barbiturate liquid containing 1 grain per 5 c.c. of probarbital (ethyl-isopropylbarbituric acid).

tained for twenty-four hours with positive pressure through an endotracheal tube with an ordinary anesthesia bag. During the thirty-six hours from the time the boy was found and the time of the telephone call, the child had received picrotoxin repeatedly, Metrazol on several occasions, intravenous fluids, alternating 5 per cent glucose in water and 5 per cent glucose in saline. The intravenous fluids contained enough Levophed bitartrate* to maintain a fairly good blood pressure. The child was showing no signs of improvement at the end of the first thirty-six hours, so it was felt urgent that he be transferred to a hospital where he could be placed in a respirator.

The above had been the gist of the telephone call at 8:00 P.M., and one hour later the child was admitted to our local hospital where an Emerson respirator was waiting. During the one-hour period after the call I picked up a folder from my file on "Poisoning" and glanced at as many references as I could find on barbiturate poisoning. Most of these references outlined the usual treatment with picrotoxin or Metrazol, supportive measures, oxygen, etc., but several short abstracts confused me. I shall refer to these abstracts later.

When first examined, the child was completely comatose and no type of stimulus produced the slightest response. Respirations were being maintained with an anesthesia bag through an endotracheal tube. No radial or anticubital pulse could be felt, blood pressure could not be obtained, but a weak femoral and apical pulse was present. The child had been without intravenous fluids and Levophed for about one hour while being transferred to the Greensboro hospital.

Immediately on admission a polyethylene tube was placed in an ankle vein and at the same time a tracheotomy was performed. The endotracheal tube was then removed and the child placed in a respirator. Intravenous fluid was started with Levophed and soon his color was improved and he had a good bounding pulse. Before being placed in the respirator breath sounds over the entire chest seemed normal with no evidence of pulmonary edema, atelectasis, or other abnormality.

At about 10:30 P.M., thirty minutes after the child was placed in the respirator, 3 mg. of picrotoxin was given intramuscularly with no apparent effect. At this time it was noted that the child's temperature rectally was 92° F., and immediately hot-water bottles were applied to the patient in an effort to warm him. Working continuously, changing hot-water bottles in a respirator throughout the night, kept two people busy, and finally after six or eight hours the temperature had risen to 96° F. rectally. At first it was thought that hypothermia might be helpful in these patients but Nelson[1] emphasizes the importance of maintaining body temperature, stating that "Hypnotic doses of barbitals may be toxic in hypothermic animals."

When first admitted, oxygen was not administered to this child because of an article by Fazekas and Koppanyi,[2] of Georgetown University, on the prevention and treatment of acute barbiturate intoxication. In this article the following statement was made: "Routine administration of oxygen is indicated in all but the most severely depressed cases of barbiturate coma.

*Winthrop-Stearns.

In very deep coma, the respiratory centers may not be responsive to CO_2, and respiration is maintained by hypoxic stimuli arising from chemoreceptors located in the aortic arch and carotid bodies. Oxygen administration in such cases will remove the cause of the reflex stimulation of the respiratory center, and breathing may cease. Hypoxia should be guarded against, since it will synergize with the depressant effects of the barbiturates. In this connection, it may be mentioned that cyanosis and dilatation of the pupil in barbiturate poisoning are indicative of very severe poisoning.'' Later, however, it was noted that most of the other references urged the use of oxygen, and soon after admission oxygen was started with a Croupette over the child's head.

Pierotoxin was then started every thirty minutes intravenously, 3 mg. per dose increasing to 6 mg. per dose for ten doses, with no apparent effect. Occasionally, soon after an injection of pierotoxin, stimulation of the sole of the foot would cause some general jerking of the entire leg. This was the only muscular movement ever noted here in the child.

At 2:30 A.M., after ten injections of pierotoxin, two articles were found which caused a dilemma. One was an article by Mousel[3] of Seattle, Washington. Let me quote from this article: ''Mousel and Essex found that the analeptics were not only useless but actually harmful in treatment of barbiturate overdose. Schmidt wrote, 'Direct studies of the oxygen consumption of the brain in situ has shown that cerebral metabolic activity runs parallel to cerebral functional activity and that convulsants may lead to cerebral anoxia (with all its consequences) because they increase oxygen demand beyond the available supply.' Reed, Driggs, and Foote reported several deaths among patients with cardiac arrhythmia who had received fairly large doses of pierotoxin, amphetamine, and caffeine, or a combination of these drugs.''

An abstract of a similar article by Clemmesen,[4] of Copenhagen, on the treatment of barbiturate poisoning made the following statement: ''Stimulants may cause fatal hyperthermia and should generally be withheld. Gastric washing has been abandoned. In Copenhagen, a single department of the Bispebjerg Hospital cares for all cases of narcotic poisoning from the city and suburbs, handling about 800 yearly. The average stay is 3 days. This section has 4 rooms and 9 beds with oxygen and suction facilities for each bed. The staff includes psychiatrists, anesthetists and other specialists, interns, and shifts of 3 nurses. Oxygen is supplied continuously through a hollow tongue depressor. For low temperature on admission, an arch of incandescent lamps is employed a few hours.'' This abstract points out that the improved management of barbiturate and morphine poisoning has reduced hospital mortality in Copenhagen from about 25 to 1.6 per cent in six years. Figures on mortality from barbiturates in the United States vary from 5.5 to 13.4 per cent.[3]

Because of these four articles pierotoxin and stimulants were stopped at 2:30 A.M., and for the next seven hours the patient was maintained on oxygen, the respirator, and 100 c.c. of low sodium human serum albumin was administered intravenously on the recommendation of Mousel,[3] who made

the following statement: "On the supposition that cerebral edema is probably responsible for the severe complications frequently seen in barbiturate poisoning, a therapeutic plan has been formulated for the treatment of these patients with 25 per cent salt-poor human serum albumin. Three patients with severe barbiturate intoxication have been successfully treated since 1949; all were treated with analeptic drugs before the serum albumin was administered, and in each instance the analeptics failed to improve the patient's condition."

After the child died Dr. Mousel was contacted by telephone, and he made the following very positive statements: (1) He believes that analeptics are definitely contraindicated in acute barbiturate poisoning, feeling that they may lead to cerebral anoxia; (2) oxygen is definitely indicated; (3) serum albumin, 2 units for adult, 1 unit for child, repeated in four hours, is of great benefit (he quoted a case of a patient treated that very week who was without reflexes for two days and improved in four hours after albumin); (4) sodium ion should be avoided in an effort to dehydrate the patient.

The following morning about 9:00 A.M. Dr. Jay Arena of Duke Hospital was contacted by telephone and consulted concerning this patient. He advised a continuation of analeptic drugs, with the feeling that they probably would not cause harm, and mentioned the use of human serum albumin which had already been given. Pierotoxin was resumed at about 10:00 A.M. and only given every two hours in 3 mg. doses. The child's condition seemed fairly good during the morning. The pulse remained quite good and efforts to check blood pressure showed a systolic pressure in the neighborhood of 80 or 90 and a questionable diastolic pressure, this pressure being taken by palpation. A second unit of low sodium serum albumin was to have been started but suddenly at noontime the child's color became very poor, the pulse could not be felt, and when removed from the respirator no heartbeat could be found. He was pronounced dead at 7 minutes after noon on the day following admission.

During the fifteen hours that he was in the hospital the patient had received 1,000 c.c. of 5 per cent glucose in saline and 700 c.c. of 5 per cent glucose in water, containing 1,000 mg. ascorbic acid and 4 c.c. of vitamin B complex. On the morning after admission, blood had been drawn for blood studies with the following results: CO_2, 47.5 volumes per cent (21.2 meq. per liter); serum chlorides, 148 meq. per liter; B.U.N. 18 mg. per cent. Blood was drawn for barbital level after death and later the report showed a barbiturate level between 25 and 50 mg. per cent. The barbiturate level in the urine was approximately 25 mg. per cent. Blood count on the morning after admission showed 3.72 million red blood cells, a white differential count of 53 segmentals, 8 stabs, 36 lymphocytes and 3 monocytes. Urinalysis showed yellow clear urine with 4 plus sugar. It was interesting that this urine showed bright fluorescence under a Wood's light.

After the child died a further interesting report was found by Hodges and Gilmore.[5] The following is the gist of their article: A case of severe barbiturate intoxication is reported, in which the coma was apparently prolonged by potassium depletion. Seco-

barbital sodium and phenobarbital had been taken, more than 1.2 Gm. of the former and "several tablets" of the latter. When examined the patient was in a deep stupor. No tendon reflexes were obtainable. Supportive and stimulative therapy was instituted. A potassium determination revealed the low blood level of 2.6 meq. per liter. Accordingly, intravenous administration of 1 liter of 0.1 per cent potassium chloride was started. Twelve hours later, or four and one-half days after ingestion of the barbiturates, patellar reflexes were obtained, rectal temperature had dropped from 104.2° to 100.4° F., and serum potassium level was 3.1 meq. per liter. A total of 4.5 Gm. of potassium chloride was administered intravenously within forty-eight hours, and 4 Gm. daily by mouth subsequently. Recovery followed, without the use of analeptic drugs. Six days after admission, low potassium was still evident in the electrocardiogram, the T waves being long, low, and dome-shaped, with definite prolongation of the Q-T interval.

Since the death of this child an article appeared in the *New England Journal of Medicine* on barbiturate poisoning by Ehrentheil and Marchand,[6] in which large doses of picrotoxin were used intravenously, plus amphetamine sulfate and strychnine sulfate, with recovery after ingestion of 8.3 Gm. of amobarbital.

For the busy practitioner who is suddenly faced with a desperate situation in a child or adult with severe barbiturate poisoning, I would like to ask the following questions:

(1) Should analeptic drugs be used or not?

(2) Should larger doses of human serum albumin be used?

(3) Should potassium chloride be used routinely?

(4) Should oxygen be used in the severely depressed patients?

I would also like to ask a question stimulated by a recent article on treatment of boric acid poisoning with replacement transfusion[7]:

(5) Should exchange transfusion be used in the desperately ill, severely comatose patient with barbiturate poisoning?

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EDITORIAL COMMENT
ON THE
TREATMENT OF ACUTE BARBITURATE POISONING

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THE very interesting case report and the difficulties encountered by Dr. Wilson in the management of acute barbiturate poisoning in a 4-year-old child has prompted the following editorial comments. The dilemma which exists in the treatment of such cases is well illustrated by this report and the questions which he specifically asked will be answered at the end of the editorial.

In order to highlight the problems involved in the treatment of acute barbiturate poisoning, a brief presentation of the pharmacology follows. All barbiturates, including the short-acting ones, become long-acting when large doses are given. Even thiopental sodium (Pentothal sodium), which generally is short-acting, may become long-acting when large doses or repeated doses are given. The short duration of action of thiopental has been explained on the basis of its rapid destruction. However, it is not destroyed rapidly; and according to Brodie and associates[1] therapeutic doses of Pentothal are short-acting because it is transferred from the nervous as well as other tissues to the fat depots over a period of thirty minutes to an hour. Repeated or large doses saturate these fat depots which may become important sites of storage. The fat depots may contain a concentration from five to ten times greater than that present in the plasma. The long action results from the fact that the stored barbiturate slowly re-enters the plasma and the concentration of the barbiturate in the tissue can only decline slowly.

The toxic effects of the barbiturates are primarily the result of their action on the central nervous system. Respiration is depressed early and breathing becomes slow and shallow; therefore, the minute volume is considerably decreased, and cyanosis may be prominent. The blood pressure falls relatively late in the course of barbiturate poisoning, unless a very large dose has been taken. Under this circumstance, the blood pressure may fall rapidly to shock levels. Very large doses of barbiturates not only depress the respiratory and vasomotor centers, but also the vascular smooth muscle directly. Unless proper treatment has been instituted, the blood pressure may fall to extremely low levels. The resulting hypoxia and the circulatory failure tend to intensify each other. Therefore, it is imperative to prevent the development of hypoxia as well as to maintain adequate circulation; otherwise, recovery from the barbi-

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turate depression is unduly delayed or even impossible.

Other deleterious effects of barbiturate poisoning include (1) hypostatic pneumonia, (2) depressed kidney function, (3) temperature abnormalities, (4) cerebral edema, and (5) diffuse brain damage. The shallow respiration, coupled with a low blood pressure, favor the occurrence of hypostatic pneumonia. As a result of the low blood pressure and the central antidiuretic action of barbiturates, urine formation is suppressed. This fact is important because certain barbiturates are slowly detoxified and recovery from their effects is dependent upon adequate renal function. Body temperature usually falls and the skin becomes cold, moist, and cyanotic. However, fever sometimes occurs and becomes progressively higher if bronchopneumonia or dehydration develops. Another important deleterious effect is a diffuse nonspecific cerebral lesion which probably results from the protracted severe hypoxia associated with acute severe barbiturate poisoning.

When death occurs quickly, it usually results from paralysis of the respiratory center. If death is delayed, vasomotor collapse, hypoxia, cerebral edema, disturbances in electrolyte balance, and hypostatic pneumonia are the usual contributory causes.

In the management of acute barbiturate poisoning, the aims and measures used will be discussed in an effort to elucidate the problems involved.

Removal of Unabsorbed Drug and Reduction of Further Absorption.—If the patient is conscious and if the barbiturate is taken orally, gastric lavage with warm water is indicated, provided the history suggests that sufficient quantity of the drug still remains in the stomach. In the comatose patient gastric lavage is indicated under similar conditions, but precautions against aspiration should be exercised. Sodium sulfate, 10 to 15 Gm., may be left in the stomach at the termination of the lavage in order to hasten the intestinal elimination of any unabsorbed barbiturate. In order to avoid possible regurgitation and aspiration of gastric contents, many authorities, however, do not recommend that any fluid be permitted to remain in the stomach after the lavage.

Maintenance of Respiratory Exchange and Prevention of Hypoxia.—Efforts to increase respiratory exchange should not be delayed until respiratory arrest is imminent. Corrective treatment should be instituted early in the development of hypoxia and should be continued until the patient recovers sufficiently to maintain adequate respiratory exchange and good circulation of blood. Measures which improve respiratory exchange include the use of respiratory stimulants, artificial respiration, and oxygen administration.

Opposing views exist concerning the use of analeptics as respiratory stimulants, and evidence both supporting and condemning their use can be cited. Metrazol, picrotoxin, ephedrine, and amphetamine are the analeptics most frequently used. With the exception of picrotoxin these analeptics have definite cortical stimulative action. This action is not of prime importance since cortical depression is not the cause of death. Two analeptics which particularly increase the excitability of the brain stem, thereby improving

respiration and vasomotor tone, are Metrazol and picrotoxin. These are probably the preferred analeptics in the treatment of barbiturate intoxication. They may be lifesaving but must be given in sufficient quantities to increase the activity of the respiratory and vasomotor centers in the medulla, thereby reducing or preventing the deleterious effects of hypoxia. Quantities capable of causing convulsions in the absence of barbiturate intoxication may be required in severely depressed patients. In patients poisoned with barbiturates, the initial dose of Metrazol for children ranges from 50 to 100 mg. and from 500 to 750 mg. for adults. Picrotoxin is given in doses from 0.2 to 0.3 mg. per kilogram (15 to 25 mg. in divided doses at fifteen-minute intervals for the adult with proportionately less for children, usually 3 to 6 mg.). It is important to remember that picrotoxin has a latent period of ten to fifteen minutes; failure to recognize this may result in the administration of an overdose and the appearance of convulsions with deleterious effects.

These analeptics may be given by continuous intravenous infusion, or they may be given intermittently by the intravenous or intramuscular routes at fifteen- to twenty-minute intervals. In either event, it is necessary to maintain adequate dosage schedules in order to maintain a continuous analeptic action; otherwise the secondary depressant action of the analeptics may become prominent. The intravenous route of administration is preferred over the intramuscular, since it lends itself to a more satisfactory and uniform effect and the response is easier to control. It should be emphasized again that picrotoxin possesses minimal ability to stimulate the sensorium and can produce convulsions without causing awakening or arousal of the patients.

Though it may be necessary to administer and to continue to administer large doses of analeptics, they should never be pushed to the point of causing convulsions. Convulsions increase the oxygen requirements and thus intensify and prolong the hypoxia. This is detrimental to these depressed patients. Due to this dangerous possibility, Clemmesen[2] recommends that analeptics should not be used in barbiturate poisonings and reports lower mortality values following the use of supportive treatments without analeptics. On the basis of clinical signs and observations of cerebral oxygen consumption, Schmidt[3] observed in monkeys that recovery following thiopental was distinctly more rapid when analeptics were not given than when "convulsant doses" of either Metrazol or picrotoxin were used. Mousel and Essex[4] observed that analeptics actually further depressed and even stopped respiration in cats severely depressed with thiopental (Pentothal) or sodium Amytal.

It is true that many case reports have shown that analeptics have contributed definitely to the saving of lives. This, however, does not prove that equal or even better results might not have followed the use of supportive measures such as artificial respiration and maintenance of circulation with pressor amines, blood, other fluids, etc. In fact, such a study was conducted in Denmark. In a series of poisoning cases from morphine, barbiturates, etc., the mortality was reduced from 25 to 3.7 per

cent in Denmark and to 1.6 per cent in Copenhagen by the use of supportive measures and no analepties.

Emphasis should be placed on the fact that analeptics are not necessary to maintain respiratory exchange when one of the mechanical means for artificial respiration is available. Actually, artificial respiration is preferred since adequate respiratory exchange is more likely to be achieved and there is no danger of the secondary depression of the nervous system. It should be emphasized, however, that an ever present danger of acidosis or alkalosis associated with hypo- or hyperventilation is present when artificial respiration is used. These may contribute further to the central nervous system damage. Therefore, facilities for measuring vital capacity and plasma CO_2 and pH are essential for adequate care of these patients. On an empirical basis, it appears that 95 per cent O_2 to 5 per cent CO_2 might be used with artificial respiration whenever adequate facilities to follow the blood chemistry are unavailable; though its use appears logical, no critical evaluations have been conducted on barbiturate poisoning.

It is true that administration of oxygen to the patient with a severely depressed respiratory center may stop the impulses arising from the chemoreceptors in the carotid body and thereby arrest respiration. However, it is imperative in barbiturate poisoning to prevent hypoxia, for hypoxia further depresses metabolism and intensifies the circulatory failure and depression of the central nervous system. Oxygen, therefore, should be administered to all severely depressed patients. It should be started early before hypoxia becomes intense and before the respiratory center is so severely depressed that spontaneous respiration is dependent upon the impulses arising from the carotid body. With artificial respiration, of course, there would be no danger of failure of respiration due to abolition of impulse from the carotid body. Attention should be called to the fact that administration of oxygen does much more than merely increase the available oxygen. It causes oxygen to replace the nitrogen dissolved in the plasma and in the tissue fluids and thus raises the oxygen tension to higher levels. This favors tissue metabolism which is very desirable.

Maintenance of Adequate Circulation and Blood Pressure.—Emphasis also should be placed on the fact that adequate circulation is equally important in order to maintain tissue respiration. This can be accomplished more satisfactorily by the use of agents which act directly on the smooth muscles of the arterioles than by the use of analeptics. Available drugs for this purpose include levarterenol (Levophed), methoxamine (Vasoxyl), phenylephrine (Neo-Synephrine). These drugs, which act directly on the blood vessel to increase their tone, are preferred since their action is more certain and since they do not exert a secondary depressant action upon the central nervous system. Levarterenol bitartrate, 4 mg. per liter, as a continuous intravenous infusion at a rate sufficient to maintain adequate blood pressure is recommended. Levarterenol provides moment-to-moment control, and a continuous infusion is required. When continuous intravenous infusions are

unavailable or must be interrupted, sustained effects for thirty minutes or longer can be obtained from single intravenous or intramuscular injections of methoxamine or phenylephrine; certainly, the intravenous route must be employed whenever circulation is inadequate for absorption. Ephedrine and amphetamine also are potentially useful to increase peripheral vascular tone. Large doses of ephedrine, particularly when repeated, may prove injurious by causing myocardial depression and a fall in blood pressure.

Maintenance of Nutrition, Body Fluids, and Electrolytes in Proper Balance.—In the unconscious patient, basal caloric requirements should be met and preferably should be administered by the parenteral route. Basic caloric requirements of the child 13 years of age or less may be calculated from the following formula suggested by Ordway: 25 minus age in years = calories per pound per 24 hours. Solutions available for this purpose are 5 to 10 per cent glucose in water and 5 per cent protein hydrolyzate. Gamble[5] has shown that the minimal quantity of glucose required to spare proteins and electrolyte is 3 Gm. per kilogram per twenty-four hours, which may be used as a guide for glucose administration. This quantity of glucose would be contained in 60 c.c. of 5 per cent glucose in water which would probably approach the minimal obligatory water requirements of comatose infants and children, since water loss from skin, respiratory tract, as well as in urine and feces, would be decreased. It should be recognized that adequate water is beneficial since it facilitates the renal elimination of the barbiturates.

It goes without saying that attention should be devoted to maintaining the proper electrolyte balance. The electrolyte requirements for these severely depressed patients are unknown. Therefore, it is necessary to follow the well-recognized concepts of fluid and electrolyte balance. The administration of electrolytes, especially sodium, potassium, chloride, and bicarbonate ions, should be governed if possible by analyses of the plasma. Caution should be exercised to prevent overhydration or hyperosmolarity; the latter may follow indiscriminate use of 5 per cent glucose in saline which is hypertonic.

Attention should be called to the fact[6] that serious hypopotassemia has been observed in one case of barbiturate intoxication, and that this prolonged the coma. In this patient, recovery was reported following the administration of potassium salts at a time when no other treatment was used.

It appears logical that the converse may also be true in the untreated, severely poisoned patients. It is well established that the condition of hypoxia with shock and impending death and the concomitant urine suppression will result in high potassium levels in the extracellular fluid compartment. Therefore, hydration should be established before potassium is given.

Good nursing care is essential and must be available. The patient's temperature, blood pressure, respiration, and heart rate should be regularly observed and charted. The use of suction and slight Trendelenburg position with hourly changes in the po-

sition of the patient should be incorporated along with other supportive measures in the treatment. Prophylactic use of antibiotics is recommended.

Other Measures.—One of several procedures may be used to reduce high blood concentrations and promote elimination of toxic materials from the body. These include exchange transfusions, intermittent peritoneal dialysis, and the artificial kidney. In the event renal function remains inadequate following fluid therapy and measures to improve circulation, the latter procedures are recommended. Unfortunately a team which is familiar with these procedures usually is not available. Intermittent peritoneal dialysis (peritoneal lavage) according to the method of Grollman[7] is not especially difficult and may prove lifesaving. We (Smith, Segal, and Etteldorf, unpublished) have used this procedure for as long as sixteen consecutive days in a case of uremia due to chronic renal disease. No complications could be attributed to the procedure.

ANSWERS TO SPECIFIC QUESTIONS ASKED BY DR. WILSON

At the onset we agree with Dr. Wilson that the medical literature on the treatment of poisoning by barbituric acid derivatives is highly confusing and we appreciate the dilemma which he faced. We commend Dr. Wilson for reporting this case and calling attention to the existing confusion. It appears that the child had suffered irreversible depression and damage of the central nervous system prior to the time when treatment was initiated. Consequently, no therapeutic regimen would be expected to be very satisfactory.

With regard to the use of analeptics, as we have mentioned above, there is no agreement to be found in published reports. It is to be recognized that deleterious effects can follow their use when given in excessive doses. We feel that Metrazol or picrotoxin, used as recommended in the above editorial comment, may be helpful at times. Moreover, we wish to emphasize that their use to the exclusion of supportive measures which will maintain respiration and circulation are unwise. The measures which reduce hypoxia include artificial respiration and agents to support circulations such as Levophed, Vasoxyl, and Neo-Synephrine. In severe cases, if it were a matter of choice between the analeptics and other measures to maintain respiration and circulation, we would choose the latter. It is important to remember that analeptics, if used, must be given in subconvulsive doses. Nevertheless, a sufficient quantity of these agents must be given to produce an adequate and a continuous effect.

As stated by Dr. Wilson, albumin has been recommended to reduce cerebral edema. Also in the absence of dehydration it will elevate the blood pressure by increasing the vascular volume and therby improve circulation. In our opinion, Dr. Wilson's dose of one unit repeated in four hours was adequate or perhaps more than adequate. It must be remembered that it is possible with large quantities of serum albumin to overload the circulatory system and to produce heart failure. The usually recommended dose is 2.0 c.c. per kilo-

gram, with a maximum of 60 to 80 c.c. being used to treat cerebral edema.

Potassium therapy is always indicated when there is a deficit of this ion. As has been indicated hypokalemia in barbiturate intoxication with improvement following potassium therapy has been reported. One should not overlook the fact that parenteral administration of potassium-free solutions, if continued as a supportive measure, may cause or aggravate potassium depletion. The hypercloremia of 148 meq. per liter of serum in Dr. Wilson's case indicates a marked hyperosmolarity as a result of liberal use of sodium chloride solution. It is quite logical to assume that hypokalemia, if present, was accentuated by the administration of sodium chloride and glucose solutions. Serial electrocardiography or flamephotometric analysis of the serum should be conducted because the serum potassium may be elevated in severe cases with profound depression, hypoxia, and urinary suppression. Therefore, it is advisable to hydrate the patients with 30 c.c. per kilogram of one-half or one-third strength saline and 5 per cent glucose solution before giving potassium. This ion should be administered at a rate not to exceed 3.5 meq. per kilogram per twenty-four hours.

In our opinion oxygen should be administered early and in high concentrations to all depressed patients. Proper use of artificial respiration requires measurement of vital capacity and determinations of plasma CO_2 content and pH.

Exchange transfusions may prove helpful in any severely poisoned and desperately ill patient. This is especially true in early cases when the procedure would be valuable in reducing the concentration of poison in the plasma and aid in its elimination from the body. If there is a release of the poison from body depots, such as fat in cases of barbiturate poison, the procedure may be repeated with benefit. It is questionable, in our opinion, that exchange transfusion would have been of any benefit in this case with likely irreversible central nervous system damage.

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THE EFFECT OF SPECIFIC THERAPY IN PRIMARY TUBERCULOSIS OF THE CHILD

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THE advent of potent and effective agents in the treatment of many forms of tuberculous disease has raised the question of their place in the management of primary tuberculosis in children. This disease has heretofore been considered a relatively benign condition, even in the absence of specific antimicrobial therapy.[1, 2]

To evaluate the effect of therapy in this variable condition several factors should be considered: (1) effect, both clinical and roentgenological, on the acute course of the disease; (2) effect on the development of complications, namely, progressive primary disease and particularly tuberculous meningitis; (3) the long-term effect on the development of reinfection tuberculosis.

With these considerations in mind, in 1950, at the suggestion of Dr. Harry H. Gordon, then Professor of Pediatries at the University of Colorado School of Medicine and Chief Consultant in Pediatrics at National Jewish Hospital, it was decided to study, in a controlled fashion, a series of children with uncomplicated primary tuberculosis. This investigation was discontinued in 1954 in order to join a nationwide cooperative study under the auspices of the United States Public Health Service. However, the results are significant enough to warrant their publication at this time.

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Aided by the United States Public Health Service Grant E-123 (C_3).

METHOD OF STUDY

With the generally conceded poorer prognosis of children under 3 years of age in mind,[3-5] children between 1 and 3 years of age and those between 3 and 10 years of age were considered separately. Infants under 1 year were not included because we did not feel justified in denying this highly susceptible group whatever benefits might result from chemotherapy.[6]

Children in both groups (under 3 and over 3 years old) with roentgenologically demonstrated uncomplicated primary (active) tuberculosis were alternated into the treatment and nontreatment groups. By limiting the study to "uncomplicated" primary tuberculosis, an effort was made to eliminate all children with any evidence of progressive primary disease, including those with endobronchial disease. It must be admitted, however, that since the onset of this study we have come to feel that most of those in the latter group do not have progressive disease.

The patients who qualified for the study were all hospitalized initially at either the Denver General Hospital, the Colorado General Hospital, the National Jewish Hospital, or the Denver

Children's Hospital. After discharge from the hospital they were seen in follow-up clinics at the Denver General Hospital, or the National Jewish Hospital, or were followed through correspondence with their private physician.

It was soon obvious that it was frequently difficult to tell which roentgenograms were "positive," especially among the smaller children. In addition to being seen by both of us and by the Pediatric Staff Conference at the National Jewish Hospital, all films were reviewed by Dr. R. P. Allen, Roentgenologist at the Denver Children's Hospital.*

There was a total of sixty-nine children in the study (Table I) who could be followed for periods ranging from one to five years. Thirty-five were in the 1- to 3-year-old group. There were thirty-five boys and thirty-four girls. The racial distribution was Spanish-American, thirty-nine; European, twenty-three; Negro, five; American Indian, two. Thirty-five of the children (Table I) had a history of some symptoms of disease, such as anorexia, fever, cough and pallor. Thirty-four were asymptomatic and were found to have tuberculosis on routine or contact examination. On admission nineteen children had physical findings consistent with a diagnosis of tuberculosis, namely, malnutrition, pallor, lethargy, or abnormal chest findings.

TABLE I. DESCRIPTION OF GROUP STUDIED

GROUP	SEX	RACIAL BACKGROUND	SYMPTOMS	PHYSICAL FINDINGS	LABORATORY RESULTS AT TIME OF DIAGNOSIS		
					HEMOGLOBIN	GASTRICS	TUBERCULIN SENSITIVITY
1-3 years With treatment 17 patients	Male-8 Female-9	Indian-1 SpA-10 European-6	Present-7 Absent-10	Pos.-4 Neg.-13	Above 11 Gm.-8 Below 11 Gm.-8 Not done-1	Pos.-3 Neg.-14	1:100,000-2 1:10,000-4 1:1,000-5 Pos. dil. Pos. dil. unk.-4 Patch-2
1-3 years No treatment 18 patients	Male-8 Female-10	SpA-7 Indian-1 Negro-2 European-8	Present-10 Absent-8	Pos.-6 Neg.-12	Above 11 Gm.-10 Below 11 Gm.-5 Not done-3	Pos.-2 Neg.-16	1:10,000-5 1:1,000-6 1:100-2 Pos. dil. unk.-4 Patch-1
3-10 years With treatment 17 patients	Male-12 Female-5	SpA-11 Negro-1 European-5	Present-7 Absent-10	Pos.-3 Neg.-14	Above 11 Gm.-16 Below 11 Gm.-1	Pos.-6 Neg.-11	1:10,000-6 1:1,000-5 Pos. dil. unk.-6
3-10 years No treatment 17 patients	Male-7 Female-10	SpA-11 Negro-2 European-4	Present-11 Absent-6	Pos.-6 Neg.-11	Above 11 Gm.-15 Below 11 Gm.-1 Not done-1	Pos.-4 Neg.-11 Not done-2	1:100,000-1 1:10,000-3 1:1,000-7 Pos. dil. unk.-5 PPD No. 2-1

The laboratory work done at the time of diagnosis (Table I) was not particularly revealing. The hemoglobin was above 11.0 grams in forty-nine patients and below 11.0 grams in fifteen patients. Five children had no record of a hemoglobin done at the time of

*We wish to express particular gratitude to Dr. R. P. Allen of the Denver Children's Hospital for his invaluable aid in roentgen interpretation.

diagnosis. Gastric washings taken at the time of admission were positive for acid-fast bacilli on culture in fifteen patients, negative in fifty-two, and not done in two patients. Smears were all negative.

but whatever error there is would probably be equally distributed between the treated and untreated groups.

The type of treatment employed varied with changing drugs and theories of proper treatment (Table II).

TABLE II. RESULT OF TREATMENT VERSUS NONTREATMENT

GROUP	AVERAGE DURATION OF FOLLOW-UP (MO.)	TREATMENT	COMPLICATIONS	LAPSE OF TIME FROM ONSET BEFORE APPEARANCE OF COMPLICATIONS (MO.)
1-3 years		INH-7		
With treatment	29	SM, INH, PAS-1		
17 patients		INH, SM-5	None	
		SM-1		
		SM, PAS-3		
1-3 years		*Changed to*	1-TB hip	16
No treatment	31.7	INH-1	2-progression	3 and 4
18 patients		INH, SM-5	1-obstruction of bronchus	4
		Continued on no treatment—12	1-Pott's disease	25
			1-TB meningitis	1
3-10 years		INH-5	1-atelectasis secondary to endobronch.	
With treatment	24	INH, SM-6	tubere.	3
17 patients		SM, PAS-6	1-RUL consolidation (these patients did not receive INH prior to onset of complications	2
3-10 years		*Changed to*		
No treatment	30.8	INH, SM-2	1 pos. urine culture	4
17 patients		SM, PAS-1	1 possible progression	5
		Continued on no treatment—14	1 endobronch. tubere.	2

All patients had positive tuberculin tests as follows:

O.T. 1:100,000—3 patients
O.T. 1:10,000—18 patients
O.T. 1:1,000—23 patients
O.T. 1:100—2 patients
O.T. of unknown dilution—probably 1:1,000 in nineteen patients
Vollmer patch—3 patients
PPD No. 2—1 patient

In all cases, events in the course of the disease were dated from the time of known onset. This was arbitrarily set at the time of the first known tuberculin reaction or at the time of definite onset of symptoms. Admittedly this is vague and inaccurate,

All children who were treated received some combination of streptomycin, isoniazid, and para-aminosalicylic acid for a period of nine months. No effort is made here to go into the problem of which is the most effective mode of therapy since we are only trying to compare children receiving some form of antimicrobial treatment with an equal number receiving none.

RESULTS

The most interesting results were obtained in the age group from 1 to 3 years of age (see Table II). Seven-

teen children in this age group who received a variety of antituberculous drugs were followed for an average of twenty-nine months. During this period, none of those seventeen treated children developed complications—evidences of progressive tuberculosis. In contrast there were eighteen children in this age group who did not receive any form of chemotherapy for tuberculosis. Six of these children developed, during the period of observation, complications and were then placed on antituberculous drug therapy with satisfactory response. One child had a persisting elevated sedimentation rate (60 mm.), positive gastric cultures (50 colonies), and possible increase in the size of the pulmonary lesion during four months of observation. This was considered indicative of progression and the child was started on treatment with isoniazid. Five months after onset of observation one child developed left lower lobe atelectasis with compensatory left upper lobe emphysema secondary to obstruction of the left main stem bronchus by extrinsic pressure. One child developed Pott's disease twenty-five months after the beginning of the observation period. One child showed a progressive increase in size of the pulmonary lesion over a five-month period. An Indian child developed tuberculous meningitis after only one month of observation. Another child developed tuberculosis of the hip sixteen months after starting the study.

In the group from 3 to 10 years of age seventeen children were treated with antituberculous drugs. One child developed right upper lobe atelectasis secondary to endobronchial disease after three months of therapy. Another child showed consolidation of the posterior segment of the right upper lobe after two months of therapy. Both of these children were under treatment with streptomycin and para-aminosalicylic acid in the years prior to the advent of isoniazid. In the age group from 3 to 10 years seventeen children were observed under no chemotherapy. Three of these children developed complications. One child had evidence of renal disease with a urine positive for tubercle

TABLE III. CHEST X-RAY FINDINGS IN TREATMENT VERSUS NONTREATMENT

GROUP	LESION STILL REGRESSING (MO.)	LESION STABLE	APPEARANCE OF CALCIUM
1-3 years With treatment 17 patients	1 in 9 1 in 14 1 in 8 1 in 5 1 in 4	11 in average of 11.6 mo.	Present in 8.7 mo., in 8; not present in 9
1-3 years No treatment 18 patients	1 in 28 1 in 24 1 in 12	12 in average of 14.7 mo.	Present in 9.6 mo. in 10; not present in 8
3-10 years With treatment 17 patients	1 in 38 1 in 16 1 in 15 1 in 14 4 in 12	1 at onset 8 in average of 17.1 mo.	Present in 13 mo., in 11; present at onset in 4
3-10 years No treatment 17 patients	1 in 11 2 in 10 1 in 6 1 in 5	11 in 15.4 mo.	Present in 10.4 mo., in 7; not present in 4

bacilli on culture after four months of observation. Another child had conversion of gastric specimens to positive (25 colonies on culture) and possible increase in the size of the pulmonary lesion after five months of observation. A third child had recurrent fever, an increased area of infiltration roentgenologically, and endobronchial disease during a two-month period of observation. These three children were placed on antitubercuIous drugs and made a satisfactory recovery.

An attempt was made to compare the x-ray changes in the treated and untreated groups (Table III). In all patients the time lapse was determined from the known onset of tuberculosis to stabilization of the pulmonary lesion and/or calcification. No correlation was noticed between the time lapse before stabilization and the use of antituberculous drugs, or between the appearance of calcium deposits and the different management of these cases.

None of the patients have yet been followed long enough to see what effect therapy might have on the development of reinfection'' tuberculosis.

DISCUSSION

The data presented above, sparse as they are, are highly suggestive in the 1- to 3-year-old group. There were no complications appearing in the seventeen patients who were treated, and complications developed in six of eighteen patients who were not treated. In the older age group no difference could be clearly demonstrated. It would seem desirable to continue this type of investigation in a much larger group (at least 1,000), in which a more truly randomized series is studied. Certainly it is established that the use of isoniazid is more effective in the prevention of the development of tuberculous meningitis and possibly other complications than streptomycin and PAS.[7]

The findings of this study concur with the belief of other workers in this field,[8] namely, that therapy does not change the normal course of uncomplicated primary tuberculosis either clinically or by x-ray.

SUMMARY

1. Sixty-nine children with roentgenologically positive uncomplicated primary tuberculosis in two groups (1 to 3 years and 3 to 10 years) were alternately treated with specific antituberculous agents for at least nine months.

2. The results with specific therapy in the group 1 to 3 years of age would seem suggestive enough to warrant further investigation of the desirability of therapy in this age group.

3. Specific therapy does not seem to alter the clinical or roentgen course of uncomplicated primary tuberculosis.

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CHRONIC BENIGN NEUTROPENIA IN INFANCY AND EARLY CHILDHOOD

Report of a Case With a Review of the Literature

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IT IS the purpose of this discussion to draw attention to a chronic form of neutropenia occurring in infants and toddlers, accompanied by remarkably few symptoms, and entirely devoid of the dramatic character of acute agranulocytosis as originally described by Schultz.[1] To my knowledge only fifteen cases of this syndrome have been published so far, all from Switzerland and the Scandinavian countries. I did not find it mentioned in the current American literature or in some of the leading American textbooks on pediatrics or hematology.

CASE REPORT

E. O., a white girl, born July 15, 1953, was brought to the hospital on March 13, 1954, with complaints of acute respiratory distress. She had been well until five days prior to admission, at which time she developed a laryngitis with increasing dyspnea. A few days before, both parents had been troubled with mild upper respiratory disease. The patient had been treated symptomatically at home with some syrup of ipecac and the complaints had subsided. Recrudescence of the symptoms led to admission.

The patient was the outcome of a normal first pregnancy and had never been ill before. She had been breast fed for five months and vitamin intake had been adequate. Family history was noncontributory; both parents were healthy; no consanguinity existed between them. No history of allergy could be elicited in the ancestry.

Physical Examination.—On admission the patient was found to be a well-developed and well-nourished white female who appeared acutely ill and was in extreme respiratory distress. There was no cyanosis. An inspiratory stridor was heard, and with each inspiration there was a marked sternal and intercostal retraction. The temperature was 98.8° F.; respirations were labored, frequency 34 per minute; the pulse rate was normal. The nasal mucous membranes were reddened and edematous; the pharynx was diffusely injected. Expansion of the chest was noted to be symmetrical. No dullness could be elicited on percussion; over both lungs dispersed crepitant râles were heard. Physical examination was otherwise normal. Fluoroscopic examination of the chest did not reveal any abnormalities.

Laboratory Examination.—Urinalysis was negative; intradermal tuberculin test (Mantoux 1:1,000) likewise negative. Forty-one hours after admission a blood count was done, with the following results: hemoglobin 11.4 grams per 100 ml.; red blood count 3,960,000 per cubic millimeter; white blood count 5,400 per cubic millimeter, with eosinophils 1 per cent, "stab" cells 1 per cent, *no* polymorphonuclears, lymphocytes 94 per cent, and monocytes 4 per cent. Throat culture was negative for diphtheria.

TABLE I. DIFFERENTIAL BLOOD COUNTS

DATE	Hb. (GM. PER 100 ML.)	RBC × 10^6	WBC	WHITE CELLS, PER CENT								REMARKS
				BAS.	EOS.	MYELO. METAM.	"STAB"	PMN	LYMPH.	MONO.	PLASMA	
1954												
3/15	11.4	3.96	5,400	–	1	–	–	1	94	4	–	700 mg. dihydrostreptomycin and 2,800,000 U. penicillin I.M. in 5 da.
3/17			3,800	1	1	–	2	–	83	13	–	
3/18	10.6	3.90	1,900	–	–	–	–	–	100		–	Thrombocytes 289,000 per cu. mm.
3/19			3,400	–	–	1	–	1	95	3	–	
3/20			3,200	–	3	1	–	–	81	15	–	
3/21			4,100	–	3	–	1	–	93	3	–	
3/22			5,100	–	1	–	–	3	91	5	–	
3/23			5,100	–	4	–	–	–	88	8	–	
3/24			4,700	1	2	–	–	–	84	13	–	
3/25			3,300	–	6	–	1	–	84	9	–	
3/26			5,800	–	2	–	1	–	95	2	–	
3/27			5,000	1	4	–	8	4	80	3	–	
3/29			6,400	–	5	–	–	2	93	–	–	
3/30			7,600	–	1	–	1	–	96	2	–	2 × 1½ c.c. pentnucleotide I.M. daily
3/31	10.7	4.76	5,800	–	7	–	3	1	89	–	–	
4/1			4,900	–	6	1	–	2	91	–	–	
4/2			5,500	–	4	–	1	1	92	2	–	Morbilliform exanthem; no fever
4/3			5,000	–	4	–	–	3	90	3	–	
4/5			3,300	–	4	–	–	4	88	4	–	
4/6			4,700	–	–	1	1	–	97	1	–	Fever (101° F.) and reappearance of rash, vomiting
4/7			6,400	–	1	–	5	2	87	5	–	
4/8			3,500	–	–	–	–	1	99	–	–	
4/9			4,200	–	–	–	1	1	98	–	–	Rash disappeared
4/12			6,000	–	–	–	4	–	95	1	–	
4/13			6,400	–	1	–	–	2	93	4	–	
4/14	10.9	5.06	7,500	–	3	–	1	7	88	1	–	
4/15			7,200	–	9	–	1	3	85	2	–	
4/20	11.5	3.41	7,000	–	5	–	–	3	92	–	–	
4/24	11.8	3.69	5,000	–	1	–	–	–	98	1	–	
4/26			5,600	–	5	–	–	1	92	2	–	
4/27			7,000	–	2	–	–	5	89	4	–	
5/1			7,400	1	5	–	1	2	86	5	–	
5/4	10.9	4.30	6,400	–	10	–	–	2	85	3	–	
5/10	9.6	3.56	6,100	–	9	–	3	–	79	8	1	
5/13	9.6	3.88	8,100	–	4	–	–	–	96	–	–	From this date on daily 225 mg. of stabilized ferrous chloride in drops
5/17			6,200	1	8	–	4	1	80	6	–	
5/21	10.7	3.95	8,000	–	4	–	10	7	70	9	–	
5/24			4,600	–	6	–	1	1	85	7	–	
5/28	10.6	4.28	6,300	–	5	–	3	5	75	12	–	
5/31			5,700	2	3	–	1	–	92	2	–	
6/3	11.8	3.97	6,500	–	6	–	–	2	91	1	–	
6/10			4,800	–	4	–	–	–	96	–	–	
6/14			5,700	1	4	–	–	–	90	5	–	
6/17			5,000	1	4	–	–	2	89	4	–	
6/21			6,300	–	7	–	–	–	84	4	–	
6/25			6,300	1	2	–	1	1	93	2	–	Impetigo of forehead, nose, and cheek
6/29	11.2	4.26	4,900	–	4	–	1	2	93	–	–	Thrombocytes 298,000; reticulocytes 1.4 per cent
7/1			3,700	–	3	–	1	1	93	2	–	
7/6			4,200	–	4	–	3	–	93	–	–	Impetigo cured
7/9			7,300	–	3	–	1	2	94	–	–	
7/12			6,800	–	2	–	2	1	95	–	–	
7/15			6,500	1	2	–	–	1	94	2	–	
7/19	11.7	4.00	5,700	–	4	–	–	3	83	10	–	

(*Continued on next page.*)

TABLE I.—CONT'D

DATE	HB. (GM. PER 100 ML.)	RBC × 10^6	WBC	WHITE CELLS, PER CENT								REMARKS
				BAS.	EOS.	MYELO. METAM.	"STAB"	PMN	LYMPH.	MONO.	PLASMA	
7/20	9 A.M		4,200	–	5	–	–	1	93	1	–	10 I.U. ACTH I.M.; eosinophils decreased from 137 to 17 per cu. mm. in 4 hr.
	13 P.M		5,600	–	1	1	8	19	70	1	–	
7/21			7,400	2	3	–	1	2	83	9	–	4 × 2½ I.U. ACTH I.M. daily
7/22 2 hr. after 2½ I.U. ACTH			4,900	–	–	–	7	61	32	–	–	
7/23			8,300	–	1	–	1	4	94	–	–	
7/24			6,700	–	1	–	–	4	94	1	–	
7/26			7,400	–	3	–	–	–	97	–	–	ACTH stopped
8/2	12.2	3.83	6,300	–	3	–	1	10	84	2	–	Discharged from hospital
8/27	11.8	4.68	6,500	–	2	–	3	14	77	4	–	Not fasting
10/8	12.5	4.51	8,800	–	1	–	1	11	84	3	–	Not fasting
12/3	13.1	4.19	8,000	1	4	–	1	7	86	1	–	Not fasting
1955												
5/13	11.3	4.13	5,200	–	2	–	1	9	84	4	–	Not fasting

The condition was diagnosed as an acute obstructive laryngitis with beginning descending tracheobronchitis.

Course.—Treatment was started immediately with the croup kettle. The patient was put on intramuscular penicillin, six times 100,000 I.U., and dihydrostreptomycin, two times 75 mg. daily. Intravenous injection of hypertonic glucose solution (50 ml. 25 per cent) did not relieve the condition. Twenty-five milligrams of phenobarbital was injected to combat the fretfulness. The temperature stayed normal; the dyspnea increased, and on palpation the pulse could not be felt during inspiration. The following days the dyspnea decreased somewhat in intensity and the baby developed a nonproductive cough reminiscent of pertussis. (There had been no contact with pertussis cases.) On the fifth day after admission she finally became much better and showed only a mild respiratory distress. It should be clearly stated that the first blood count mentioned above was made after the baby had received 900,000 I.U. of penicillin and 300 mg. of dihydrostreptomycin intramuscularly. A second blood count was performed on the fifth hospital day; the findings were: white blood count 3,800 per cubic millimeter, with eosinophils 1 per cent, basophils 1 per cent, "stab" cells 2 per cent, lymphocytes 83 per cent, and monocytes 13 per cent. Penicillin and dihydrostreptomycin were stopped. The next day the blood count was as follows: hemoglobin 10.6 grams per 100 ml.; red blood count 3,900,000 per cubic millimeter; white blood count 1,900 per cubic millimeter, with no granulocytes; thrombocytes 289,000 per cubic millimeter (Fonio); bleeding time 1½ minutes; clotting time 2¼ minutes. Physical examination was normal except for a slight inspiratory stridor.

A bone marrow sample from the left iliac crest was taken; the marrow was of normal cellularity; no abnormal cells were found. There were no signs of a "maturation arrest," but there was a relative increase in elements of the myeloid series, with a relatively low percentage of mature polymorphonuclears, as may be seen from Table II.

Subsequent blood counts were made almost daily for the next four weeks and twice weekly thereafter for about three and one-half months. In Table I the pertinent data can be found, and in Fig. 1 the findings, expressed as totals per cubic millimeter are depicted.*

*Blood counts were made in the morning before the first meal.

On the thirteenth hospital day the baby was started upon a course of Pentnucleotide in intramuscular injections of 1½ ml. twice daily. The peripheral blood count showed a slight increase in granulocytes, almost at once followed by a drop to previous levels. Moreover, a generalized nonitching papulomacular exanthem manifested itself, accompanied by a marked rash in the diaper area. The exanthem was interpreted as a drug eruption due to Pentnucleotide (the only drug the child was receiving at that moment) and it was discontinued, the more so as it apparently was without influence on the neutrophil count. During the rash the peripheral eosinophil count was low, and there existed no eosinophilia of the bone marrow. After discontinuation of the drug the rash decreased in intensity, only to reappear full blown a few days afterward. In retrospect I do not believe that the eruption was due to any drug at all, but that it more or less is part of the clinical picture, as was pointed out by Ström.[2] With the exception of the exanthem, the child did not show any abnormalities on physical examination. She ate and drank well, was active, and apparently quite happy. At one time she had a mild coryza, during which episode there was a slight *increase* in granulocytes, eosinophils, and lymphocytes in the peripheral blood. A few days afterward the neutrophils again dropped to their previous extremely low levels. The baby did rather well, but her weight curve expressed a marked hydrolability. The diaper rash healed and relapsed and for some time there was a rather obstinate contagious impetigo in the face.

On July 20, 1954, the effect of intramuscular adrenocorticotropic hormone was studied, the idea behind this being to try to imitate the effect of "stress" on the neutropenia. Ten I.U. of ACTH was injected; the eosinophils dropped from 260 to 17 per cubic

TABLE II. DIFFERENTIAL BONE MARROW COUNTS; SAMPLES TAKEN FROM LEFT ILIAC CREST

DATE	3/18/54	4/2/54	4/16/54	6/12/54	7/16/54
Myeloblasts %	1.25	2.00	2.2	1.6	4.0
Promyelocytes %	2.25	1.00	1.4	1.2	2.2
Myelocytes, neutrophilic %	18.75	17.75	19.2	16.4	25.8
Metamyelocytes, neutrophilic %	23.50	18.25	20.8	20.6	15.4
"Stab" cells, neutrophilic %	25.00	15.50	26.0	18.6	16.6
Polymorphonuclear neutrophils %	5.25	4.50	4.4	6.4	1.6
Total neutrophils %	76.00	59.00	74.0	64.8	65.6
Myelocytes, eosinophilic %	1.00	1.00	1.0	1.6	0.4
Metamyelocytes, eosinophilic %	0.75	1.00	0.2	1.0	0.0
Polymorphonuclear eosinophils %	0.25	0.25	0.4	1.0	0.0
Total eosinophils %	2.00	2.25	1.6	3.6	0.4
Total basophils %	0.00	0.00	0.00	0.2	0.0
Total myeloid series	78.00	61.25	75.6	68.6	66.0
Lymphocytes %	2.25	27.50	8.8	16.8	18.2
Plasma cells %	0.25	0.00	0.0	0.0	0.0
Monocytes %	0.25	0.25	0.0	0.0	0.0
Pronormoblasts ("macroblasts") %	0.00	0.00	0.2	0.4	0.4
Normoblasts, basophilic %	6.50	2.75	3.6	4.8	5.2
Normoblasts, polychromatophilic %	7.50	3.00	10.8	7.8	7.2
Normoblasts, acidophilic %	5.25	5.25	1.0	1.4	2.6
Total erythroid series	19.25	11.00	15.6	14.4	15.4
Reticulum cells %	0.00	0.00	0.0	0.2	0.0
Megakaryocytes	Normal	Normal	Normal	Normal	Normal
Myeloid:erythroid ratio	4.1	5.8	5.0	4.5	4.3
Mitotic figures %	0.5	1.2	0.6	0.2	0.4
Cellularity	Normal	Normal	Normal	Normal	Normal
Abnormal cells	None	None	None	None	None

millimeter within four hours, and in the same time the total white blood count rose from 4,200 per cubic millimeter with 1 per cent granulocytes to 5,600 per cubic millimeter with 28 per cent granulocytes, the increase in circulating leukocytes apparently being due entirely to an increase in neutrophils. However, twenty-four hours afterward the neutrophils again had cent granulocytes! But this success was very short lived; the next day almost no granulocytes could be detected on the slide six hours after the injection.

On July 29, 1954, the effect of 10 I.U. was restudied, with essentially the same results as mentioned before (Table III). From this study it was felt likely that in case of an acute

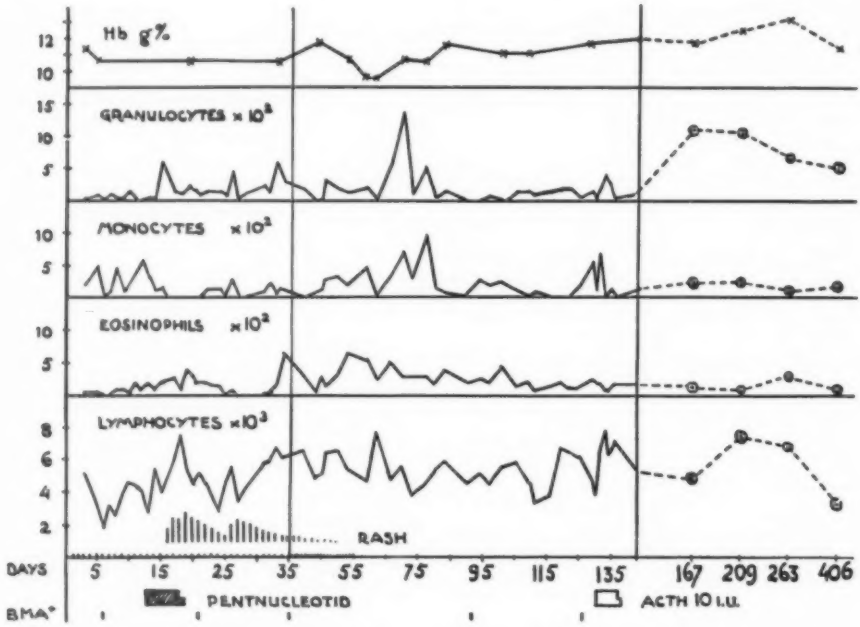

Fig. 1.—*BMA, Bone marrow aspiration; all specimens taken from the left iliac crest.

Table III. Effect of Intramuscular Injection of 10 I.U. of ACTH

7/28/54	Eosinophils per cu. mm.	WBC	Polymorphonuclears	
			per cent	per cu. mm.
Before injection	289	5,500	7	385
After 2 hr.	173	7,500	27	2,025
After 4 hr.	119	5,600	25	1,400
After 6 hr.	85	5,900	8	472

practically disappeared from the peripheral circulation.

From now on the baby was on a course of intramuscular ACTH, 2½ I.U. q.i.d. Six hours after the first injection the white blood count was 4,900 per cubic millimeter with 68 per

infection, the child would be able to draw on the neutrophils to play their defensive role. She was discharged on Aug. 3, 1954, at the age of 1 year. Her weight was 9,860 grams; eight incisors had erupted; she walked with support and spoke a few words. No

outward signs of illness could be detected. Spleen and lymph glands had never been palpable. From May 13, 1954, on she had been placed on ferrous chloride for a mild hypochromic anemia; meanwhile the hemoglobin had risen to 12.3 grams per 100 ml.

After discharge she was seen on various occasions in the outpatient clinic. She was examined last on Jan. 25, 1956; by then she was 30 months of age, weight being 12.5 kilograms and length 90 cm. She had cut twenty teeth. Blood count was as follows: hemoglobin 13.1 grams per 100 ml.; red blood count 4,050,000 per cubic millimeter; white blood count 3,800 per cubic millimeter; thrombocytes 162,000 per cubic millimeter; reticulocytes 8 per 1,000 red cells. Though there still existed a leukopenia the differential count was almost normal: eosinophils 3 per cent, "stab" cells 6 per cent, polymorphonuclears 19 per cent, lymphocytes 71 per cent, monocytes 1 per cent.

With the exception of an occasional sore throat she had been doing well; during the episodes of pharyngitis she had shown repeatedly a leukocytosis with a normal neutrophil count. Except for a mild tonsillar hypertrophy, physical examination was negative. The Central Laboratory of the Netherlands' Red Cross Blood Transfusion Service (Director: Dr. J. J. van Loghem, Jr.) performed a blood typing and investigated the possibility of leukoagglutinins in the child's serum being the cause of the granulocytopenia. The blood group was: A, ccDEe (Rh_2/rh), MN. The serum complement titer was normal. No specific immune antibodies were found; leukoagglutinins were absent.

On Aug. 27, 1954, a blood count was done on both parents, the results being: Father: hemoglobin 15.7 grams per 100 ml.; red blood count 4,910,000 per cubic millimeter; white blood count 5,700 per cubic millimeter, with eosinophils 1 per cent, basophils 1 per cent, "stab" cells 3 per cent, polymorphonuclears 70 per cent, lymphocytes 17 per cent, monocytes 8 per cent. Mother: hemoglobin 12.8 grams per 100 ml.; red blood count 4,640,000 per cubic millimeter; white blood count 6,300 per cubic millimeter, with eosinophils 1 per cent, polymorphonuclears 65 per cent, lymphocytes 32 per cent, monocytes 2 per cent.

REVIEW OF THE LITERATURE

Fanconi[3] in 1941 was the first to report a case of "chronic benign agranulocytosis in infancy" in a 7-month-old girl. Since then cases have been described by Tobler and Buser-Plüss,[4] Fanconi[5] (two cases), Salomonsen,[6] Ström,[2] Rohr,[7] Vrtilek,[8] who reviewed the three cases already reported by Fanconi and added three of his own, Gasser,[9] who made an extensive review of the bone marrow picture in this condition by restudying the six cases encountered in the Zürich pediatric department and who added one more case, and finally by Vahlquist and Anjou[10] (four cases).

The pertinent data gathered from this review of the literature are to be found in Table IV. As will be seen, no mention is made of the size of spleen, liver, and lymph nodes. This item was purposely omitted from Table IV on account of its inconsistency, only the Swiss authors making occasional mention of a transient enlargement of these organs, and that merely during an intercurrent infection. In most cases it is stated explicitly that splenomegaly, hepatomegaly, or an increase in the size of the palpable lymph nodes was not encountered. They do not seem to belong to the clinical picture.

TABLE IV. COMPOSITE SURVEY OF

CASE NUMBER	AUTHOR(S) AND YEAR OF PUBLICATION	SEX	AGE WHEN DIAGNOSIS WAS MADE	MAIN SYMPTOMS				DRUGS USED BEFORE DIAGNOSIS WAS MADE	TOTAL AMOUNT IN GRAMS	ALLERGY		PERIPHERAL BLOOD						
				REPEATED RESPIRATORY INFECTIONS	PYODERMA	RASHES	ANOREXIA, VOMITING			IN PATIENT	IN FAMILY	WBC	GRANULOCYTES	EOSINOPHILS	MONOCYTES	LYMPHOCYTES	ANEMIA	THROMBOCYTES
1.	Fanconi, 1941 (Vrtilek, 1952)	F	7 mo.	+	–	–	–	Py	0.6	+	n. m.	D	D	N	TI	I	–	N
2.	Tobler and Buser-Plüss, 1942	M	10½ mo.	+	+	–	–	ST	±25	n. m.	n. m.	N	D	N	I	N	+	I
3.	Fanconi, 1946 (Vrtilek, 1952) a	F	6 mo.	+		+	–	Somnocodal	?	+	n. m.	D	D	D	TI	D	–	TD
4.	b	M	12 mo.	+	–	–	+	SM	?	–	–	D	D	N	TI	I	–	N
5.	Salomonsen, 1948	F	9½ mo.	+	–	–	+	ST	2	–	–	D	D	N	I	N	–	N
6.	Ström, 1949	M	15 mo.	+	+	+	–	S	?	–	–	D	D	N	N	N	–	N
7.	Hotz (Rohr), 1949	M	5¼ mo.	–	+	–	–	n. m.	n. m.	–	–	D	D	N	N	D	+	N
8.	Vrtilek, 1952 a	F	7 mo.	+	–	–	–	Py ST	0.6 1.5	–	–	D	D	N	TI	I	–	N
9.	b	F	8 mo.	+	–	+	+	SM	?	+	+	D	D	N	TI	I	–	N
10.	c	M	2½ yr.	+	–	–	+	Py ST Ir	0.5 1.5 4.0	+	–	D	D	TD	TI	D	+	N
11.	Gasser, 1952	F	15 mo.	+	–	–	+	–	–	–	–	D	D	N	N	N	–	N
12.	Vahlquist and Anjeu, 1952 a	F	8½ mo.	–	–	+	–	–	–	–	–	D	D	N	N	N	–	N
13.	b	F	6 yr.	+	–	–	–	S	?	–	–	D	D	N	N	N	–	N
14.	c	M	9 mo.	+	–	–	–	S, Pen. Sal.	5	–	+	D	D	TI	N	N	+	N
15.	d	M	20 mo.	+	+	+	–	SA	?	–	+	D	D	TI	I	N	+	N
16.	Present author	F	8 mo.	+	+	+	+	Pen. DHS.	0.3	–	–	D	D	TD	TD	N	±	N

N = normal; D = decreased; TD = temporary decrease; I = increase; TI = temporary increase; n.m. = not mentioned.

Py = Pyramidon; ST = sulfathiazole; SM = sulfamerazine; SA = sulfonamide; S = sulfa drug, character not given; Ir = irgafen; Pen. = penicillin; Sal. = salicylate; Dhs = dihydrostreptomycin; Adr. = Adrenalin.

DATA FROM LITERATURE

BONE MARROW												REACTIONS OF GRANULOCYTES TO DRUGS				
CELLULARITY	MATURATION ARREST IN PREMYELOTIC-MYELOCYTIC STAGE	RELATIVE DECREASE OF MATURE GRANULOCYTES	PHAGOCYTOSIS OF GRANULOCYTES BY MONOCYTES	EOSINOPHILS	MONOCYTES	ERYTHROPOIESIS	MEGAKARYOCYTES	RETICULUM CELLS	DURATION OF GRANULOCYTOPENIA	REACTION TO INFECTIONS	PENTNUCLEOTIDE	SULFONAMIDES	OTHERS	FINAL OUTCOME OR CONDITION WHEN SEEN LAST	REMARKS
N	±	+	+	N	N	TD	N	N	4 mo.	n.m.	None	–	–	Cured	When 7 yr. old acute erythroblastopenia during attack of diphtheria; spontaneous cure
N	–	Temp.	–	N	N	D	N	N	>7 mo.	TI+ monocytes	None	TI	–	Cured	Compensating monocytosis No leukocidins in serum
D	+	+	–	D→ Abs.	N	D	N	N	5 yr.	TI	n.m.	n.m.	–	Died	Panmyelo. phthisis
N	–	+	+	N	N	TD	N	N	4 yr.	n.m.	–	–	–	Cured	Mental and physical deficiency
I	–	±	–	N	N	N	N	N	1½ yr.	None	None	–	–	Cured	
I	–	+	–	N	N	N	N	N	1 yr.	TI	–	–	–	Cured	
I	+	+	–	I	N	N	N	N	>6 mo.	n.m.	n.m.	n.m.	n.m.	Cured	
N	–	+	–	N	N	TD	N	N	1 yr.	–	–	–	–	Cured	
N	+	+	–	I	N	TD	N	N	1 yr.	None	–	–	–	Cured	
N	–	+	–	I	N	TD	N	N	±1 yr.	TI	–	–	–	Cured	Mental and physical deficiency; macrocephaly
N	–	+	+	N	N	N	N	N	8 mo.	n.m.	n.m.	n.m.	n.m.	Cured	No incomplete antibodies
N	–	+	–	I	N	D	N	N	10 mo.	n.m.	None	–	–	Cured	
I	+	±	–	N	N	N	N	N	>2 yr.	n.m.	None	TI	Adr. TI	Cured	Mental deficiency No leukocidins in serum
N	+	+	–	N	N	N	N	I	?	n.m.	n.m.	n.m.	–	Cured	
I	+	–	–	N	N	N	N	I	>11½ yr.	n.m.	TI	TI	–	Granulocytopenia	
N	–	+	–	N	N	N	N	N	>15 mo.	TI	None	–	ACTH TI	Granulocytopenia	No leukoagglutinins in serum

DIAGNOSIS

The case report given fits in well with the clinical picture of "chronic benign neutropenia in infancy and early childhood" as described by the authors mentioned.* Salomonsen[6] was the first to express the opinion that this syndrome ought to be considered a distinct clinical entity. As criteria for diagnosis he postulated:

1. Chronic, marked, selective granulocytopenia with a corresponding leukopenia
2. Normal bone marrow
3. Lowered resistance to infections, but otherwise little constitutional involvement
4. Resistance to medicaments commonly employed in the treatment of granulocytopenia
5. Spontaneous cure

Of these criteria the chronic, marked, selective neutropenia was found in all cases. The one case in which there also existed an aneosinophilia ended fatally (Case 3). Apparently, disappearance of the eosinophils from the blood and the bone marrow is a prognostically unfavorable sign.

The lowered resistance to infections is likewise found in all cases as might be expected. Still, in the case reported here, the child did not differ markedly from "normal" children of the same age group in this respect. I doubt whether this criterion alone would lead one to the right diagnosis.

With the "medicaments commonly employed in the treatment of granulocytopenia" presumably the sulfonamides, penicillin, and Pentnucleotide were meant. The first two exert no specific action in any case of agranulocytosis, and only serve to bridge the gap in the body's defense against bacteriemia during the leukopenic state. Pentnucleotide is reported to have caused a transient rise in the neutrophil count in Case 15. In all other cases where it was tried it was of no avail.

As to the fifth criterion of Salomonsen's, the "spontaneous cure," this can only be used for diagnosis in retrospect.

His second criterion, the "normal bone marrow," merits a more elaborate comment. As to the qualitative aspects it is agreed by all who studied the disease that there were never any abnormal cells found.

Cellularity appeared normal or increased, with the exception of Case 3 in its later stage of panmyelophthisis.

The myeloid-erythroid ratio was increased in most cases, but it is not clear whether this was due to an increase in elements of the myeloid series, a decrease in erythroid elements, or both. A "shift to the left" in the erythroid series was never clearly demonstrated.

Hyperplasia of reticuloendothelial elements is mentioned only in Cases 14 and 15; the patient in Case 15 at least was very chronic and still showed a neutropenia after eleven and one-half years (the duration in Case 14 is not given). It is possible that in cases of outspoken chronicity a reactive reticuloendothelial hyperplasia plays a part.

The monocytes were never found to be increased in the bone marrow, notwithstanding the fact that a peripheral monocytosis was noted fairly frequently. Apparently these blood monocytes originated from extramedullary centers; in Tobler's case they were shown to possess a marked phagocytotic activity.

In three cases (1, 4, 11) mention is made of phagocytosis of neutrophils

*I prefer the term "neutropenia" to that of "granulocytopenia" since, as a rule, *only* the neutrophils are involved.

by monocytes in the bone marrow. This phenomenon was only rarely encountered and did not seem to play a major part in the causation of the relative decrease in mature neutrophils. In the case reported here this phenomenon was searched for industriously; it was not encountered, however.

A feature found in all case reports is a *relative decrease in mature bone marrow neutrophils;* at least, this is the way in which it is commonly reported. For reasons indicated below it perhaps would be better to speak of a *relative increase in "stab" cells,* often accompanied by a rise in metamyelocytes and myelocytes as well. A relative increase in premyelocytes was only occasionally encountered, and then as a merely transient phenomenon. As a rule, this shift in the ratio between "stab" cells and segmented neutrophils does not become manifest until a differential bone marrow count has been done and even then it depends upon what one is going to consider a normal percentage distribution. By using Opitz' composite table[11] of percentages of different cell types to be found in the medulla of the one-year-old, I consistently noted a relative increase in "stab" cells, metamyelocytes, and myelocytes. This increase was small, however.

Gasser[9] concluded from this phenomenon to a peculiar type of "maturation arrest" in the ripening of the segmented neutrophils as the main cause of the neutropenia in this syndrome. As will be seen, the effect of intramuscular ACTH in the case reported here led to the assumption, not of a "maturation arrest," but of an increased segregation of neutrophils from the blood stream.

Taking it all together, it may be stated that in cases of chronic benign neutropenia the bone marrow picture is almost normal, with the exception of a slight relative increase in "stab" cells, metamyelocytes, myelocytes, and, occasionally, premyelocytes. Erythropoiesis is normal or may appear somewhat depressed; platelet formation is normal. There may be an increase in reticuloendothelial cells. The monocyte count is normal notwithstanding the often noted blood monocytosis; occasional phagocytosis of neutrophils by monocytes is seen.

From this discussion it will be clear that the main point in diagnosis remains the "chronic, marked, selective neutropenia."

ETIOLOGY AND PATHOGENESIS

The problem of the etiology of "chronic benign neutropenia in infancy and early childhood" remains unsolved as yet.

An innate weakness of the neutrophils,[3] hypersensitivity to certain drugs,[6] repeated infections,[8, 9] allergy,[8] the infantile tendency to lymphatic reactions,[7] and a possible disturbance of the vegetative diencephalic centers leading to an increased parasympathetic activity,[9] all variously have been incriminated. Where specifically looked for, none of these mechanisms was proved to be operating, however.

In no case did consanguinity exist between the parents; leukopenia in ancestors or siblings was not found; there was apparently no difference in sex incidence.

In most cases specific mention was made of an arrest in the maturation of the segmented neutrophils and thus the neutropenia was considered to be a sequence of the decreased production of polymorphonuclears. However, if

a maturation arrest were the real cause of the neutropenic state it would seem difficult to conceive that only two hours after the injection of adrenocorticotropic hormone a normal peripheral neutrophil count could be reached (Table III), since the maturation of the neutrophil is rather a time-taking process, the total development taking about eight days.[12] Therefore it may be concluded that in this condition there are sufficient mature neutrophils available for instant use in case some "stress" should be exerted upon the body. But, once having been "called to the lines," *these neutrophils disappear with increased rapidity from the circulation.* The normal lifespan of the blood neutrophil was shown by Osgood[13] to be about two and one-half days under experimental conditions; according to Moeschlin[12] it exists in the peripheral blood from *two to four days.* As can be seen from Table III, however, the preinjection level of the neutrophil count was reached again *within six hours* after intramuscular ACTH. Now the possibility of an exaggerate leukocyte destruction in the peripheral blood has been put to the test by searching for serum leukocidins,[4, 10] immune autoantibodies (Gasser[9], present author), and leukoagglutinins (this case), all with negative results. An abnormal fragility of the neutrophils was looked for by Vahlquist and Anjou[10] without success.

Since until now no mechanism accounting for an increased destruction of segmented neutrophils in the peripheral blood itself has been discovered, it seems logical to look at the reticuloendothelial system, and to the spleen in particular, as a cause of the accelerated removal of circulating polymorphonuclears. This possibility has been rejected by most authors since the clinical picture does not show much resemblance to the "primary splenic neutropenia" as described by Wiseman and Doan.[14] Accordingly, splenectomy has not been performed in any of these cases.

Still, in this case the experiments with ACTH rather point in the direction of a (temporary) hyperfunction of the spleen, and possibly of the rest of the reticuloendothelial system as well, especially in so far as it is concerned with the segregation and sequestration of mature neutrophils. The bone marrow apparently tries to overcome the shortage by increased production and this explains the relative increase in "stab" cells, metamyelocytes, and myelocytes. An analogy of what happens in this condition might be found in cases of chronic thrombocytopenia in young children: as a rule little constitutional involvement, a moderate increase in immature, so-called "intermediate," megakaryocytes (not by far the enormous increase in these cells encountered in adult thrombocytopenia), and a tendency to spontaneous healing. Likewise, in idiopathic thrombocytopenia in the young child, splenectomy is not often indicated.[15]

Be this as it may, the only thing that can be done to throw more light on this peculiar condition is to collect more data. It is hoped that this case report will be of some help in looking for it.

SUMMARY

A case is described of "chronic benign neutropenia" in a female infant 8 months of age. The peripheral blood constantly showed a marked, selective neutropenia; the bone marrow was characterized by only a slight

degree of increase in young neutrophils, as contrasted with a low normal percentage of polymorphonuclears. Otherwise the bone marrow picture was normal. There was little constitutional involvement after the complaint for which she had been taken to hospital, namely, acute descending laryngotracheobronchitis, had subsided. Spleen, liver, and lymph nodes were never found to be enlarged. The child reacted to infections with a transient rise in circulating neutrophils; injection of ACTH had the same effect. Pentnucleotide did not cure the condition. The cause remained undetermined.

The bone marrow picture in this condition is generally considered to show some degree of "maturation arrest" at the stage of the young neutrophils. However, intramuscular injection of ACTH caused the number of circulating neutrophils to rise to normal levels within two hours, a phenomenon difficult to explain on the basis of a "maturation arrest." In the case reported here it was shown that the polymorphonuclears disappeared from the blood stream with increased rapidity, but there were never found any factors operating in the peripheral blood itself which might lead to increased destruction there. This directs the attention to a selective hyperfunction of the reticuloendothelial system, and of the spleen in particular, resulting in an accelerated removal of the segmented neutrophils from the circulation. This predominance of leukocyte segregation and sequestration over leukocyte production might act as a stimulus to the bone marrow; hence, the increase in young neutrophils.

An analogy of this condition might be seen in chronic idiopathic thrombocytopenia in young children, which also shows comparatively little constitutional involvement, a moderate increase in slightly immature "thrombocyte precursors," i.e., megakaryocytes, and a tendency to spontaneous healing.

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ABSORPTION OF OILY AND AQUEOUS PREPARATIONS OF TETRACYCLINE IN CHILDREN

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TETRACYCLINE is available in both oily and aqueous preparations for oral use in pediatric practice. No previous data being available on the relative absorption of these products in children, the study reported in this paper was made.*

METHODS

Both types of the tetracycline were in the form of pediatric drops containing 100 mg. per milliliter. They were administered in a single oral dose of 17.6 mg. per kilogram of body weight. Twenty children were used, one-half receiving the antibiotic in oil and the other half in water. All were under 2 years of age. Venous blood was taken at 2, 4, and 8 hours. It was allowed to clot and the tetracycline determined in 24 hours or less. Sera which were not assayed at once were stored at 4° C. Assays were carried out by a method which was essentially that described by English[1] in which *Streptococcus pyogenes*, ATCC 8668, was the test organism. A control containing pooled human serum in the same amount as the experimental specimen was run with each group of sera. Each specimen was done in duplicate. Blood was taken for assay at 12 and 24 hours on an additional six children.

RESULTS

Table I shows the results of administering tetracycline in oil to ten children and in water to ten others. Considerable variation is seen in the serum levels attained by different children given the same dose in the same vehicle. However, there is no difference in the median of the levels of one group as compared to the other. The peak tetracycline concentration is reached between 2 and 4 hours with either preparation. Serum levels in six additional children were determined at 12 and 24 hours. Values are shown in Table I. Since there was no difference between values obtained with either preparation, the mean of all the concentrations obtained at 2, 4, 8, 12, and 24 hours were calculated and graphed as shown in Fig. 1. These studies indicate that 17.6 mg. per kilogram in a single oral dose will maintain levels for 12 but not 24 hours, equal to the minimum inhibiting in vitro concentration of most bacteria encountered.[2] This level may be achieved with either the oil or water preparation of tetracycline. Similar values to those found in this study have been reported by Finland and associates,[3] Schwazer and co-workers,[4] and Wood and associates,[5] using an aqueous solution. No reac-

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This investigation was supported in part by The Upjohn Company.

*The tetracycline was furnished through the courtesy of Dr. James A. Dugger of The Upjohn Company.

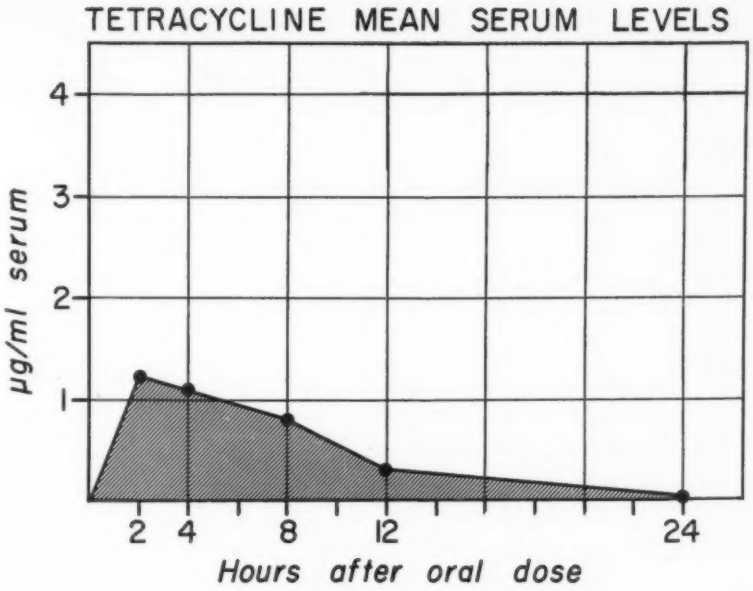

Fig. 1.

TABLE I. SERUM CONCENTRATIONS OF TETRACYCLINE IN CHILDREN RECEIVING 17.6 MG. PER KILOGRAM IN A SINGLE ORAL DOSE

PATIENT	AGE (MO.)	2 HR.	4 HR.	8 HR.	12 HR.	24 HR.
			In Oil			
1	2	.312	1.248	.624		
2	2	.624	.624	<.156		
3	1	.312	.624	.312		
4	2	1.248	2.496	2.496		
5	11	.624	.312	<.156		
6	12	.624	1.248	.624		
7	24	1.248	.624	<.156		
8	2	2.490	2.496	.624		
9	5	.624	.624	.624 (6)		
10	4	.312	.624	.312 (6)		
11	12				.624	<.156
12	1				<.156	.156
13	2				.156	----
14	12				.312	<.156
Median		.624	.624	.468		
Mean		.841	1.098	.585*		
			In Water			
15	7	2.496	1.248	.624		
16	4	1.248	1.248	.624		
17	3	.624	.312	.156		
18	3	.624	.624	<.156		
19	3	4.99	2.496	2.496		
20	4	.624	.624	.312		
21	9	.312	<.156	<.156		
22	5	.624	.312	.312		
23	8	4.99	4.99	4.99		
24	13	.156	.312	<.156		
25	6				.312	<.156
26	3				.312	<.156
Median		.624	.624	.312		
Mean		1.668	1.23	.975*		

*Mean calculated using <1.56 = .078.

Two values given under 8 hours in oil were obtained with serum collected at 6 hours.

tions such as diarrhea or vomiting were observed in any of the patients studied.

A further finding was made with reference to tetracycline levels in newborn infants. The three studied were unusually high at both 12 and 24 hours with the same dosage as used in the other studies. Values were as follows:

Patient	*μG/ml. of tetracycline*	
	12 hr.	*24 hr.*
1 (aqueous)	1.248	1.248
2 (aqueous)	4.99	1.248
3 (oil)	2.496	1.248

This was not due to any bacteriostatic substance in the blood of these children, as blood from five newborn infants who had not been given tetracycline showed no inhibitory action on the test organism. Further investigations of this phenomenon would seem to be warranted.

SUMMARY

A single oral dose of tetracycline is absorbed equally well by children in either an aqueous solution or an oily suspension. Peak levels are attained between 2 and 4 hours. Lower, but in most cases, inhibitory concentrations persist for 8 to 12 hours.

We wish to thank Dr. Clare Sun, Grace H. Meade, and William Franklin for technical assistance in this study.

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Personal Fumigation

The Select Men of Portsmouth have built a Fence a-cross the Main Road, at the Entrance of that Town, and erected a small Building, in order to smoke all Persons from Boston [where the smallpox prevailed] . . . and that constant Attendance will be given at said Smoke House for that Purpose from five o'Clock in the Morning till Ten at Night; also if any Person shall presume to come into that Town from Boston, without a Certificate of his being so smoked, he shall be immediately taken up and confined.

From BOSTON EVENING POST, March 19, 1764.

THE DAILY CIRCULATING EOSINOPHIL RESPONSE AS A GUIDE TO ADEQUACY OF HORMONE THERAPY IN ACTIVE RHEUMATIC CARDITIS

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IN RECENT reports on hormone therapy in active rheumatic carditis, there is increasing emphasis on the importance of early and adequate therapy. However, the daily dosage and duration of therapy are still controversial.[1, 2] In our studies (1949-1955) on the effect of short-term therapy in active rheumatic carditis, it was concluded that overt residual cardiac damage did not result when patients were given adequate hormone therapy early in the disease for an average period of seven days.[3, 4] The circulating eosinophil response was observed to be a guide to the adequacy of dosage. The present report is concerned with a comparison of the clinical course and the daily circulating eosinophil response during and following therapy at various dosages of hormone in terms of body weight.

MATERIAL AND METHODS

The daily circulating eosinophil response was reviewed in forty-eight patient attacks of active carditis. Hormones were given for an average period of seven days. Only patients in whom the daily circulating eosinophil counts had been adequately documented during and for one week following therapy were included. The technique used has been previously described.[3*] Blood was drawn each morning four hours after the last medication. Hormones were given daily in divided doses, every six hours, for seven days. The total dosage for each preparation included: ACTH by intramuscular injection, from 173 to 650 mg.; the oral administration of compound E, from 2,200 to 2,800 mg.; and of compound F, from 1,450 to 2,120 mg.

The patients ranged in age from 4½ to 19 years. The majority were under 14 years of age. The body weight ranged from 19 to 84 kilograms. The diagnostic criteria used for the presence and termination of active carditis have been previously described and follow the criteria of the American Heart Association.[4] Patients treated within ten days of onset were considered "early" in contrast to those treated "late," two to three weeks after onset. A recurrence of symptoms and signs of active carditis was considered a "recurrence." Recurring fever and arthralgia for one to four days, unaccompanied by carditis, were termed a "rebound."

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This study was aided by grants from The Commonwealth Fund and the Helen Hay Whitney Foundation.

*It is recognized that there are diurnal variations in circulating eosinophils. The technique used and the experience of the examiner must also be considered. In these studies an experienced examiner performed the test each morning. Variations between two chamber counts rarely exceeded 10 cells in counts below 50; in higher counts, variations ranged from 10 to 15 cells.

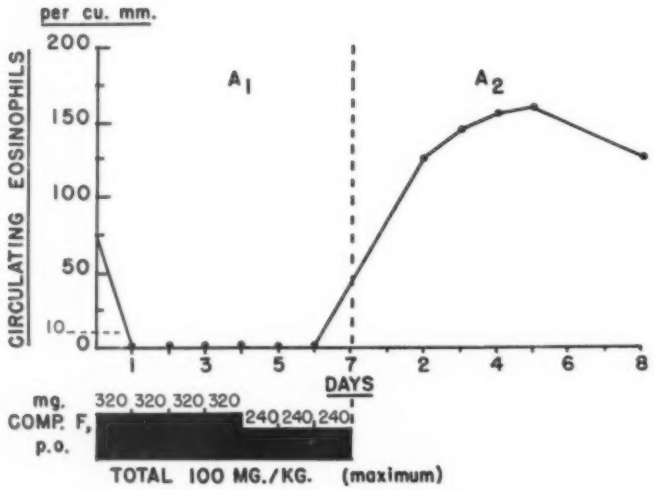

Fig. 1.—Patient J. E., 8 years of age, weight 19.6 kilograms. Initial attack, moderately severe acute carditis. Treated with compound F on seventh day of illness in maximum dosage per kilogram of body weight. Ambulatory ten days after cessation of therapy; no evidence of cardiac damage.

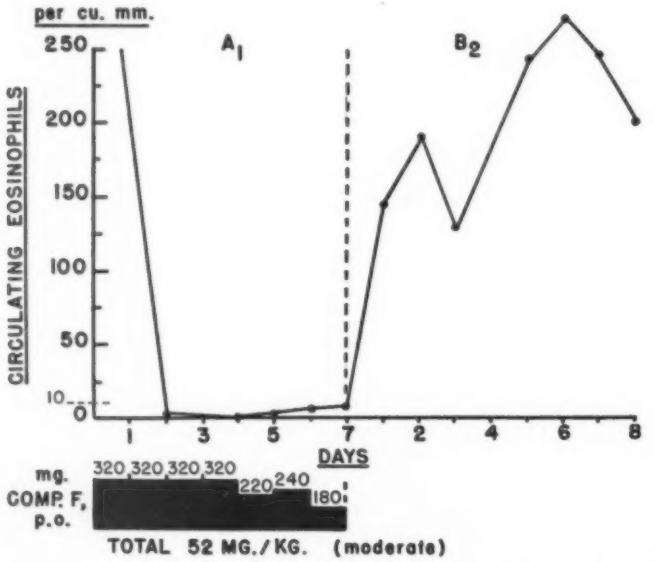

Fig. 2.—Patient C. S., 9½ years of age, weight 36.7 kilograms. Recurrent attack of mild carditis. Treated on seventh day of illness with compound F in moderate dosage per kilogram of body weight. Ambulatory seven days after cessation of treatment; no evidence of increased cardiac damage.

OBSERVATIONS

The daily circulating eosinophil response during therapy may best be presented graphically. The circulating eosinophils remained below 10 per cubic millimeter for the entire week of treatment (Fig. 1) in twenty-nine patients. In nine patients, they remained below 10 per cubic millimeter for the first four to five days and rose above 10 per cubic millimeter during the last two to three days of treatment as shown in Fig. 2. In ten patients, the circulating eosinophils fluctuated above 10 per cubic millimeter during therapy as illustrated in Fig. 3.

In order to determine whether the amount of hormone required bore a direct relation to body weight, the total amount received for seven days, as well as the daily dosage, was calculated per kilogram of body weight. Since there was no significant difference in clinical or circulating eosinophil response to the three types of hormone used, they were combined for analysis. The total dosage received may be described as minimum, moderate, or maximum (Table I).

Recurrence of Carditis Related to Adequacy of Therapy.—The circulating eosinophil and clinical response at each level of dosage is presented in Table II. It will be seen that thirty-eight patients with circulating eosinophil response pattern A or B experienced two recurrences on minimum dosage and no recurrence on moderate or maximum dosage. The two patients experiencing a recurrence had been

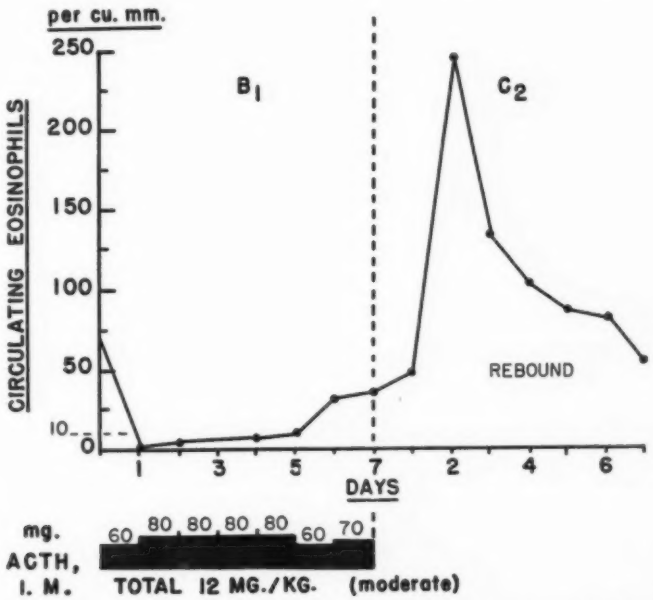

Fig. 3.—Patient T. M., 10 years of age, weight 37 kilograms. Presumably initial attack, severe carditis. Treated on twenty-first day of illness with ACTH, intramuscularly, in moderate dosage per kilogram of body weight. Rebound (fever and arthralgia) four days after cessation of treatment. Residual equivocal cardiac enlargement.

treated early in the course. Of the ten patients whose circulating eosinophil count during therapy fluctuated above 10 per cubic millimeter (C_1), six were on minimum and four on moderate dosage, with four and one recurrence, respectively. All of these patients had been treated early in the course. It is significant that of seven patients who experienced a recurrence, six had received minimum dosage. When the total dosage received was calculated by body weight, the majority of patients had received moderate or maximum amounts.

Any complicating stressful situation was found to temporarily depress the circulating eosinophils. Tapering or the omission of any dose was reflected in a rise of the circulating eosinophils.

TABLE I. TOTAL HORMONE THERAPY PER KILOGRAM OF BODY WEIGHT

HORMONE		DOSAGE								
		DAILY RANGE	TOTAL FOR 7 DAYS							
			RANGE	MINIMUM		MODERATE		MAXIMUM		
TYPE	TOTAL NO.	MG.	MG.	MG./KG.	NO.	MG./KG.	NO.	MG./KG.	NO.	
ACTH, I.M.	23	2-5.5	173-650	4-10	9	10-20	9	20-30	5	
Cortisone, p.o.	6	8-17	2,200-2,800	30-50	3	50-75	1	75-100	2	
Hydrocortisone, p.o.	19	7-16	1,450-2,120	38-50	5	50-75	11	75-100	3	
Total	48				17		21		10	

TABLE II. CIRCULATING EOSINOPHIL AND CLINICAL RESPONSE TO DOSAGE OF HORMONE

TYPE	TOTAL NO.	REBOUND	RECURRENCE	DOSAGE								
				MINIMUM			MODERATE			MAXIMUM		
				TOTAL NO.	REBOUND	RECURRENCE	TOTAL NO.	REBOUND	RECURRENCE	TOTAL NO.	REBOUND	RECURRENCE
A_1	29	8	1	7	3	1	14	4	0	8	1	0
B_1	9	3	1	4	1	1	5	2	0	0	0	0
C_1	10	1	5	6	0	4	4	1	1	0	0	0
Total	48	12	7	17	4	6	23	7	1	8	1	

In this and subsequent tables, *rebound* is defined as fever and arthralgia for a few days unaccompanied by carditis, and *recurrence* as recurrence of symptoms and signs of active carditis.

A_1 = Circulating eosinophils remaining below 10 per cubic millimeter for entire week.

B_1 = Circulating eosinophils remaining below 10 per cubic millimeter for first four to five days, then rising toward or above 10 per cubic millimeter in last two to three days.

C_1 = Circulating eosinophils fluctuating above 10 per cubic millimeter during seven-day treatment period.

TABLE III. SHORT-TERM HORMONE THERAPY
(Average 7 Days)

HORMONE	DAIL DOSAGE (MG.)	DURATION (DAYS)
ACTH, I.M.	100 (25 q 6 h.)	4
	80 (20 q 6 h.)	3
Compound E	400 (100 q 6 h.)	4
	320 (80 q 6 h.)	3
Compound F	320 (80 q 6 h.)	4
	240 (60 q 6 h.)	3

The effective dosage of hormone required was determined by trial and error (Table III).

Rebound and Post-therapeutic Circulating Eosinophil Response.—An analysis of the post-therapeutic cir-

culating eosinophil response in relation to early- and late-treated patients is of interest. It was characterized in thirty-two patients by a gradual or sharp rise in the first three to four days followed either by a slight decline, or remaining approximately within the normal range of 80 to 500 per cubic millimeter (Fig. 1). In sixteen patients there was a continuous decline after an initial rise (Fig. 2).

In the first series of thirty-two patients (Table IV), it may be seen that there were five, or 16 per cent, rebounds, four of the rebounds occurring in late-treated cases. Of the sixteen patients with the C_2 circulating eosinophil pattern (Fig. 4), seven, or

TABLE IV. POST-THERAPEUTIC CIRCULATING EOSINOPHIL RESPONSE IN EARLY- AND LATE-TREATED CASES

CIRC. EOS. PATTERN	TOTAL NO.	EARLY CASES*			LATE CASES†		
		TOTAL NO.	REBOUND	RECURRENCE	TOTAL NO.	REBOUND	RECURRENCE
A_2 and B_2	32	16	1	1	16	4	1
C_2	16	8	2	6	8	5	0
Total	48	24	3	7	24	9	1

*_Early cases:_ therapy within ten days of onset.

†_Late cases:_ therapy within two to three weeks of onset.

A_2 and B_2 = A gradual or sharp rise of circulating eosinophils in the first three to four days, followed either by a slight decline or remaining within normal range (80 to 500).

C_2 = A continuous decline of circulating eosinophils after an initial rise.

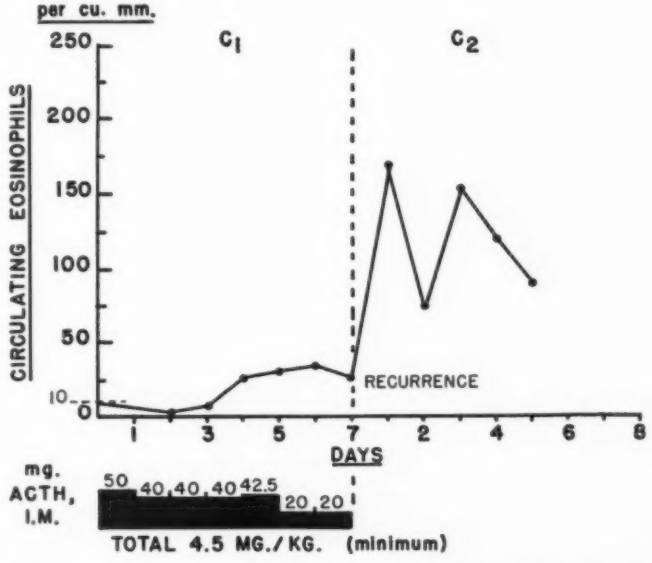

Fig. 4.—Patient J. A., 11 years of age, weight 56 kilograms. Recurrent attack of very severe carditis. Treated on sixth day of illness with ACTH, intramuscularly, in minimum dosage per kilogram of body weight. Recurrence on last day of therapy. Retreated with ACTH in maximum dosage. Ambulatory two weeks after cessation of therapy; no evidence of increased cardiac damage.

44 per cent, experienced rebounds and five of these were in the late-treated group. Rebounds occurred in the majority of patients who were treated late, irrespective of dosage.

COMMENT

During the study period the optimum daily dosage was reached by trial and error. When the daily and total amount received is related to body weight it is apparent that the majority of patients received moderate or maximum amounts. The daily amount far exceeds the dosage reported in the majority of studies. It is significant that only one patient experienced a recurrence of carditis on moderate dosage, compared to recurrences in the majority of patients receiving minimum dosage. Inadequate dosage was reflected in the circulating eosinophil response during therapy and presaged a recurrence even though patients were treated early in the course.

A comparison of the incidence of rebounds in early- and late-treated cases revealed that the majority of the latter experienced rebounds irrespective of dosage received. A characteristic post-therapeutic eosinophil pattern was observed in these patients.

SUMMARY AND CONCLUSIONS

1. It would seem reasonable to conclude that the daily circulating eosinophil response during therapy reflects adequacy of dosage.

2. The post-therapeutic eosinophil pattern presages a rebound in the late-treated cases.

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CONSEQUENCES OF NEONATAL PATHOLOGY

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CURRENT interest in cerebral palsy has led several investigators to make careful studies of prenatal and birth histories of brain-damaged children. Most of these have been retrograde studies. In order to get a better perspective of what actually happens when newborn and young infants are victims of disease and injury, three different groups of babies have been investigated at Children's Hospital in San Francisco. Two of these are follow-up studies and one is retrograde, as follows: (1) Infants from the newborn nurseries who at birth or during the hospital stay had symptoms or signs that might indicate central nervous system injury or disease. (2) Newborn and young infants admitted to the pediatric or contagious disease units with disease that might produce damage to the central nervous system. (3) Children in the cerebral palsy clinic born at the hospital and whose newborn records are comparable with the above group (1).

MATERIAL

Children's Hospital is a general hospital admitting primarily women and children. In addition to the usual departments, it has a contagious disease unit. The newborn nurseries are under the direction of the department of pediatrics but there is a close liaison between obstetrics and pediatrics. The pediatric resident is in attendance at cesarean and abnormal deliveries. Joint discussions are held on resuscitation, replacement transfusions, and fatal cases. In a previous study[1] it was found that 90 per cent of deliveries were performed by physicians limiting practice to obstetrics. The other 10 per cent were done by a limited number of general practitioners well trained in obstetrics. Approximately 90 per cent were private patients. Since January, 1952, the resident on the nurseries has kept a file on newborn infants showing any abnormality while in the nursery. From this file was selected the material for Group I of this study. These infants now range in age from 6 months to 3½ years. It is obvious that observation over such a short period of time is insufficient. These patients require observation their entire life span. It is possible that late psychological manifestations or even longevity may be influenced by birth injury.

During the period from Jan. 1, 1952, to July 1, 1955, there were 6,687 babies delivered at the hospital (Table I). Of these, 6,610 were born alive, seventy-seven were stillborn, 460 were premature births. There were ninety-four neonatal deaths of which sixty-six were premature and twenty-eight were at term. There were fifty-five infants

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who had conditions or symptoms which might indicate future brain abnormality or deficit. This study is not designed to review the fatal cases, but two types of fatalities were deemed pertinent to this study. There were twelve deaths from erythroblastosis; eight of these were stillborn and four died shortly after birth before or in spite of transfusion; one of these latter was a premature and three were at term. There were seven deaths due to intracranial hemorrhage. Three of these were premature infants and four were at term.

GROUP I. NEWBORN INFANTS FROM THE OBSTETRICAL NURSERIES

Fifty-five newborns who might be candidates for central nervous system damage have had follow-up studies. This was done by contacting the pediatrician or physician in charge at the time the infant was in the nursery. Most of the babies were under the care of staff physicians. On fifty-one of the fifty-five satisfactory follow-up was possible. Six patients were found to be handicapped and forty-seven had no sequelae referable to the newborn symptomatology that could be determined by pediatric evaluation. These babies are subdivided according to type of pathology in four groups (Tables II, III, IV, and V). In Table II are fourteen cases of blood dyscrasia. It was impossible to locate one of these. Of the thirteen remaining, eight had erythroblastosis, four of whom had exchange blood transfusions, and one of the others was ABO incompatibility, with no transfusion. The others had two, three, and four small nonexchange transfusions. One of these erythroblastotic infants is severely handicapped. There were five with other types of blood dyscrasia. Two were hemorrhagic disease of the newborn. One was a severe anemia believed from blood studies to be due to blood loss, probably from the cord or placenta before delivery. One patient had thrombocytopenic purpura. This infant developed extensive petechiae and ecchymosis shortly after delivery and had several convulsions. She was transfused and given cortisone. She recovered but has blindness and a moderate left hemiplegia. The mother was found also to have a thrombocytopenic purpura. One infant had hemolytic anemia; the type could not be satisfactorily determined. It may have been on the basis of infection. This child has impaired hearing and marked atonia. The latter two babies are in the cerebral palsy clinic. Dr. Ralph Wallerstein has made all the hematological studies on the above group.

TABLE I. CHILDREN'S HOSPITAL STATISTICS, JAN. 1, 1952, TO JUNE 30, 1955

Babies delivered		6,687
Born alive (prematures—460)	6,610	
Stillborn (erythroblastotic—8)	77	
Neonatal deaths		94
At term (erythroblastotic—3)	28	
Premature (erythroblastotic—1)	66	
Neonates relative to present study		55

Table III is an analysis of children sustaining head injury during delivery. There were twelve in this group and follow-up studies were obtainable on all except one. There were four known skull fractures demonstrated

TABLE II. NEONATES WITH BLOOD DYSCRASIA

TYPE	NUMBER	THERAPY		SEQUELAE		RECOVERY	UNKNOWN
Erythroblastosis fetalis	8	Exchange transfusion	4			7	
		Multiple transfusion	3	Retarded	1		
		No therapy	1				
Hemorrhagic disease of newborn	2	Transfused	2		0	2	
Icterus and anemia—type undetermined	1	Exchange transfusion	1	Deafness and atonia	1	0	
Thrombocytopenic purpura	1	Transfusion, cortisone	1	Blindness and hemiplegia	1	0	
Anemia—intrauterine hemorrhage cord or placenta	1	Transfusion	1		0	1	
Not followed	1	–	–		–	–	1
Total	14				3	10	1

TABLE III. NEONATES WITH HEAD TRAUMA

TYPE		SEQUELAE	RECOVERY	UNKNOWN
Skull fracture	4	0	4	
Depressed	1			
Comminuted and depressed	1			
Linear	2			
Cephalhematoma (no x-ray)	4	0	4	
Paresis	3	0	3	
Left internal strabismus	1			
Right arm	1			
Left facial	2			
Convulsions in conjunction with above paresis	3			
Subdural hematoma	1	–	–	1
Total	12	0	11	1

TABLE IV. NEONATES WITH RESPIRATORY DISTRESS

TYPE		THERAPY		SEQUELAE	RECOVERY	UNKNOWN
		OXYGEN	ANTIBIOTICS			
Anoxic—requiring resuscitation	4	4	2	0	4	
Atelectatic	6	6	5	0	6	
Pneumonia	3	3	3	0	3	
Pneumothorax	1	1	1	0	1	
Not followed	2	–	–	–	–	2
Total	16	14	11	0	14	2

TABLE V. NEONATAL DISEASE—MISCELLANEOUS GROUP

TYPE		SEQUELAE	RECOVERY
Convulsions—unknown etiology	2	1	1
Marasmic	2	1	1
Post-mortem delivery	1	0	1
Tremors, opisthotonus irritability	3	0	3
Survivor twin set (sibling macerated)	3	1	2
Survivor twin set—premature, enteritis	1	0	1
Diabetic mother	1	0	1
Total	13	3	10

TABLE VI. HOSPITAL ADMISSIONS—NEONATES AND INFANTS WITH DISEASE

TYPE		AGE	SEQUELAE		RECOVERY
Birth trauma (convulsions, skull fracture)	1	Newborn	Right hemiplegia	1	0
Survivor—macerated twin (convulsions)	1	Newborn	Quadriplegia, microcephaly	1	0
Erythroblastosis (transfusions)	1	Newborn		0	1
Convulsions—unknown etiology	3	Newborn		0	3
Severe generalized infections	2	Under 7 wk.	Severe retardation	1	1
Meningitis	3	Under 6 mo.	Retardation	2	1
Encephalitis	1	Under 6 mo.	Retardation	1	0
Total	12			6	6

by x-ray, two of which were depressed and one was comminuted. Four other infants had large cephalhematomas, but did not have x-rays taken of the skull. Three children had paresis, two of the face and one of the arm. Three of the children in the group had convulsions during the nursery period. None of the eleven followed had any nervous system sequelae, even though the one with comminuted fracture, now 3 years of age, has had craniotomy.

Table IV is an analysis of neonates having respiratory distress during the newborn period. There were sixteen infants in this group; on two no follow-up was obtained. Among the others there were four babies with intrauterine anoxia due in two instances to premature separation of the placenta, in one to premedication, and in one to long difficult labor. There were six cases of atelectasis, one of which had unilateral emphysema. There were three patients with pneumonia and one with pneumothorax. Two of the children were in the Airlock, one for two hours, and the other for seven hours. All of these infants had oxygen therapy, the time varying from one to seven days. Eleven of them had some form of antibiotic therapy. None of this group has any demonstrable evidence of central nervous system damage.

Table V consists of a miscellaneous but interesting group of babies. One infant was delivered by post-mortem cesarean section. The mother had streptococcic meningitis secondary to rupture of an old cerebral abscess. This child is normal. Two children were born at term, weighing three pounds 4 ounces, and 3 pounds 15 ounces, respectively. These both looked marasmic and in each case the placenta showed extensive infarcts. One of these children has slight hemiatrophy and curious small, fragile hands. Her mentality is normal. The other child at 3 years is normal though of small stature. Two children had convulsions of unknown etiology. One of these is normal, the other continued to have convulsions and was found later by pneumoencephalograms to have a brain defect, probably on the basis of congenital anomaly. Three children with hyperexcitability, tremors, and opisthotonus are normal. The child of a diabetic mother is normal. One very small premature infant, 1 pound 15 ounces, with bloody stools, is normal. There were three instances in which one of twins was macerated at birth. Two of these surviving twins are normal, but the other is a microcephalic, spastic quadriplegia. The latter child had no demonstrable evidence of injury in the nursery and like the other two was dismissed as normal. There were, therefore, three children in this miscellaneous group who were abnormal.

GROUP II. NEONATES AND INFANTS ADMITTED TO THE HOSPITAL WITH DISEASE

There were twelve newborn and young infants admitted to the pediatric or contagious disease wards with disturbances which might cause central nervous system damage. These are analyzed in Table VI. Six of these were admitted in the neonatal period, the remainder were admitted under 6 months of age. Of the neonates four were hospitalized for convulsions, one of these had skull fracture, cephalhematomas, and facial paresis. This

child is in the cerebral palsy clinic with a right hemiplegia. She has a normal intelligence. Another whose twin sibling was born macerated was admitted because of the occurrence of convulsions. He is now a microcephalic quadriplegia. The remaining two with convulsions of unknown etiology are normal except that one has a recurrent urinary tract infection. One child with neonatal erythroblastosis is normal. Two of the infants had severe generalized infection, sepsis, diarrhea, or pneumonia. One of these is severely retarded, the other is normal. There were three with meningitis, two of whom have central nervous system sequelae and one is normal. One child with encephalitis is severely retarded. Direct damage to the central nervous system by infection or intoxication has a serious effect in the young—50 per cent of these infants on our service have central nervous system sequelae.

GROUP III. CHILDREN IN THE CEREBRAL PALSY CLINIC BORN IN CHILDREN'S HOSPITAL

The final group analyzed were eighteen children attending the cerebral palsy clinic who were born at this hospital and whose early histories and physical examinations in the nursery afforded comparison with Group I. These eighteen patients are analyzed in Table VII. There were seven premature infants in the group; of these five were of pairs of twins, three were surviving twins, and two represented a set of twins. Of the other two premature infants, one had congenital heart disease. This infant while in the hospital and once after dismissal had prolonged apneic episodes, which attacks were believed, after careful study, to be secondary to the cardiac condition. The other one had a severe apneic attack in the nursery for which intracardiac Adrenalin was adminis-

TABLE VII. CHILDREN WITH CEREBRAL PALSY—STUDY OF BIRTH RECORDS FOR BRAIN-DAMAGE PREDICTABILITY

			PREDICTABLE IN NURSERY	NOT PREDICTABLE IN NURSERY
Blood dyscrasia		2	1	1
Injuries—trauma at birth		2	2	0
Prematures		7	3	4
Twin (one of set)	3			
Both twins	2			
Congenital heart	1			
Apnea—intracardiac stimulation	1			
Surviving twin at term (Sibling dead in utero)		1	0	1
Congenital deformities		4	3	1
Arrested hydrocephalus	1			
Hydrocephalus	1			
Strabismus only in nursery	1			
Congenital defect central nervous system	1			
(Congenital heart and premature, see above)				
Undiagnosed		2	–	2
Total		18	9	9

tered. One had beginning evidence of retrolental fibroplasia. The other four were dismissed in good condition. The pair of illegitimate twins appeared later with a history of gross neglect in the home, one having sustained a skull fracture and subdural hematoma. Of the two others dismissed apparently in good condition, one is a severe athetoid and the other is primarily a slow developer with atonic muscles and delayed bone age. One child survived whose twin sibling was macerated in utero. This infant is a microcephalic, spastic quadriplegia. There are two similar children in our cerebral palsy clinic.

Two children born at term represent sequelae of birth trauma. One of these, a severe athetoid, was a first child; the mother suffered vascular collapse with an unobtainable blood pressure while being given caudal anesthesia. Delivery was difficult. The infant was slow to breathe, had a weak, feeble cry, and several days elapsed before there was any sucking reflex. The second child was delivered after a long labor following a persistent posterior position. Like the other infant this baby had a weak, feeble cry and many days elapsed before the sucking reflex returned. This infant has cortical visual disturbance and delayed walking.

Five congenital anomalies occurred in the group. One of these died early. One has hydrocephalus. One has arrested hydrocephalus with mental retardation. One other is retarded and a slow developer. One with congenital heart disease has been described with the premature infants above. Three of these gave concern in the nursery. Of the other two, one was noted merely to have a peculiar shaped head (arrested hydrocephalus) and the other a persistent strabismus. Two of the children in the cerebral palsy clinic are the results of blood dyscrasia reported above in Group I.

There were two children in whom the cause of the central nervous system abnormality is still unknown; both of these were unrecognized as abnormal in the nursery. One is a severe athetoid and one is a retarded, autistic child.

In nine of the eighteen children (50 per cent) registered in our brain-damaged group there was no specific evidence in the nursery that they would have severe central nervous system symptoms later. In only two of these (the neglected twins) is there evidence that the damage was caused later. One infant was noted to have a persistent strabismus, but this was insufficient to interfere in the placement of the child for adoption. The possibility of a surviving twin being abnormal when the sibling died in utero is an observation made on our own material, and commented on elsewhere.[1]

DISCUSSION

The present study represents a search for the basic etiology in brain damage. It is obvious that retrograde studies of cerebral palsy alone will not give an accurate picture of neonates' reactions to different types of stress. Three facts are impressive in these tables. The first of these might be descriptively stated as, "Babies are designed to live." Newborn infants with a good prenatal history, born at term, are sturdy, robust individuals and can recuperate from considerable shock, trauma, infection, and other distress. None of the babies with head

injury or respiratory disease in the nursery had evidence of persistent brain damage at the time of the follow-up. As stated earlier, this does not preclude possible later consequences from perinatal pathology.

The second fact might be covered with the phrase, "Neonates have a past history." The present investigation and other studies reveal that premature and feeble infants often have a poor past history which indicates adverse genetic factors, isoimmunization, or an intrauterine environment unfavorable to normal development of the fetus. A maternal history of abortions, stillbirths or previous premature births may indicate a short or morbid life span for the infant that survives. Prematurity, multiple births with resultant deprivation of one or both infants of either oxygen or adequate nutrition, death in utero of one of twins, congenital anomalies, and isoimmunizations are frequently associated with brain defects. It is often impossible to separate pre- and postnatal conditions; the latter is usually related and consequential to the former. It is also impossible to separate completely one set of symptoms from another; these, too, are interrelated. Atelectasis, pneumonia, or emphysema may be secondary to anoxia in utero, to medication of the mother, trauma during delivery, or to external factors. Perinatal pathology is well reviewed in the symposium on anoxia in newborn infants.[2]

Finally, direct attack on the central nervous system of newborn or young infants by infection, or by bacterial or other toxins, results in injury in a large percentage of cases.

SUMMARY

Three groups of babies have been studied. (1) A follow-up study on fifty-one of fifty-five infants born in Children's Hospital has been made and resulted in forty-five found to be developing normally and six being handicapped. (2) Of twelve infants admitted to the hospital with diseases that might produce central nervous system sequelae, 50 per cent were found on follow-up to be handicapped. (3) The birth records of eighteen children in the cerebral palsy clinic, born at Children's Hospital, were studied. In nine, or 50 per cent, there was no evidence in the nursery that the infants would be handicapped. Prematurity, blood dyscrasias, and infection played the major role in handicapping the infants in this series. A full-term baby with a good prenatal history is a robust individual and tends to recuperate fully from the stress of being born, even when this is prolonged and traumatic. This series of cases is small; it is hoped more studies of this type will be done.

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INFANTILE CORTICAL HYPEROSTOSIS

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IT WAS originally thought that infantile cortical hyperostosis, often called Caffey's disease, was a rare disease. It appears that it is more common than is generally known. Sidbury and Sidbury[44] in 1954 reported ten cases from a private practice over a four-year period and point out that there are now sixty-nine cases reported in the medical literature.

Sherman and Hellyer,[28] after reviewing their x-ray films of infants for the preceding twenty years, suggested that this syndrome is either new or that the incidence has rapidly increased in recent years. The disease has been encountered in almost all parts of this country and all over the world, without regard to social level or ethnic groups. However, it appears that it is not well known to the medical profession in general. Therefore, it is justified to add eleven cases of infantile cortical hyperostosis to the cases already reported. These cases were observed at Children's Medical Center in Dallas, Texas, during the last six years. They represent infants who were 2½ to 6 months old on admission to the hospital. Seven of them were white, four of them Negroes.

Infantile cortical hyperostosis was described by Caffey and Silverman[2] in 1945. It was so named because of the age incidence and the biopsy findings of hyperplasia of the cortical bone without subperiosteal hemorrhage to account for the periosteal elevation. Probably the first case was described in Germany, by Roske[1] in 1930 but the syndrome was not appreciated until the publication of the clinical and roentgenologic picture.

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CLINICAL PICTURE

Familial occurrence of infantile cortical hyperostosis in utero has been discussed by Barba and Freriks.[38] They diagnosed this condition in two siblings during separate pregnancies, by means of roentgenograms. The demonstration of prenatal infantile cortical hyperostosis, in Caffey's opinion, is one of the most important observations made in this disease. He states that it has been shown conclusively that the lesions develop in some cases many weeks before birth. He mentions one of his patients whose lesions were present on the first day of life and were well advanced ten days later. Bennett and Nelson[40] described a case in which the features of infantile cortical hyperostosis were demonstrated radiologically in utero.

The clinical picture invariably begins during the first half year of life. Age seems to be a decisive factor in diagnosis. Indeed Caffey believes that an onset after 6 months of age is reason for questioning the diagnosis.

Fig. 1.—Typical facial appearance in mandibular type of infantile cortical hyperostosis. Case 1.

Fig. 2.—Striking mandibular involvement of infantile cortical hyperostosis. Note bilateral clavicular disease. Case 1.

The onset of infantile cortical hyperostosis is usually sudden in an infant previously apparently well, whose nutritional status is characteristically good. Its major general features consist of fever, hyperirritability, pallor, and upset feeding habits. These general symptoms frequently precede the clinical evidence of bone involvement. The soft tissues over the bone are fixed and very tender. There is usually no erythema or increased warmth of the overlying skin. Motion of the involved part is limited by pain, and pseudoparalysis may be present. The mandible is not involved in all cases as was originally believed. If it is involved there is swelling over the jaws, which gives a typical moon-shaped appearance to the face. This feature is easily recognizable by the clinician. Fig. 1 shows this facial appearance well. Fig. 2 is the radiograph of this patient, showing striking mandibular and some clavicular involvement. Other swelling may involve the bones of the extremities. If the ribs are involved, there may be pleural effusion. One or several bones may be affected at the same time. The regional lymph nodes are not enlarged. The size of the swelling varies markedly as the disease progresses through exacerbations and remissions.

Table I shows the distribution of bone involvement in these eleven cases. The percentages are only of relative value. Probably involvement of other bones was not detected because complete roentgenologic studies were not made in all cases.

TABLE I. DISTRIBUTION OF BONE INVOLVEMENT IN THIS SERIES

BONES INVOLVED	NUMBER OF CASES
Mandible	8
Humerus	4
Ulna	4
Ribs	4
Clavicle	4
Femur	2
Scapula	2
Radius	2
Tibia	2
Fibula	2
Metatarsals	1
Metacarpals	1

PROGNOSIS

The prognosis for life is good. The symptoms usually persist for several months. The bone changes often increase or new lesions appear after the clinical symptoms subside and then gradually disappear in one or two years. However, there is a picture of chronic infantile cortical hyperostosis. Caffey described some late skeletal changes and reports on a girl who at 22 months of age, nineteen months after the onset of infantile cortical hyperostosis, showed bony bridges between the ulna and radius and between two contiguous ribs. The elbows were swollen, pronation of the forearms was sharply limited, and the right leg was larger and longer than the left. Fig. 3 shows mandibular involvement with increased size of the bone two years later.

LABORATORY FINDINGS

All of our cases showed leukocytosis and increased sedimentation rate. Anemia and an elevated serum alkaline phosphatase were present frequently. Pertinent negative data include the serologic test for syphilis, tuberculin skin test, urinalysis, serum, calcium and inorganic phosphorus, serum vitamin A and vitamin C concentration, and sickle-cell preparations.

ETIOLOGY

The search for the etiology of this syndrome has been unrewarding. Infection was logically considered first, because of the findings of anemia, leukocytosis, elevated sedimentation rate, fever, and a remitting course. Bacteriologic and viral investigations have been negative. There has been no evidence that trauma or endocrinopathy are etiological factors. Barba and Freriks[38] suggest that the condition represents embryonal osteodysgenesis consequent to a local defect in the vascular supply. Sidbury and Sidbury[44] believe that infantile cortical hyperostosis is the clinical manifestation of an inherited defect of the arterioles supplying the affected areas. The resulting hypoxia causes focal necrosis of the overlying soft tissues and proliferative reaction of the periosteum. Bowman and associates[48] believe that infantile cortical hyperostosis results from an allergic phenomenon wherein edema and inflammatory reaction cause elevation of the periosteum and the deposition of calcium.

S. L. Eversole* at Johns Hopkins Hospital has studied pathologically five cases of Caffey's disease with biopsies of the involved bones. He found that the earliest lesions show extensive acute inflammation with polymorphonuclear cells in large numbers. This process extends through the periosteum into the surrounding soft tissue. Later this process subsides and there are caps of new bone overlying the normal bone. This later also is present in large amounts, i.e., increased numbers of trabeculae, and there is scarring of the marrow.

A. *B.*

Fig. 3.—*A*, Acute mandibular hyperostosis. *B*, Appearance two years later. Case 8.

DIFFERENTIAL DIAGNOSIS

The general clinical symptoms are of little differential diagnostic value. Fever, irritability, and upset feeding habits are present in many diseases. In the mandibular type, mumps, pa-

*Personal communication.

rotid tumor, calculus in the parotid duct, and osteomyelitis of the mandible were suspected. In the scapular type, rickets was considered, and in the long bone type, congenital syphilis.

Syphilitic periostitis may appear to be similar to infantile cortical hyperostosis roentgenologically. In fact, the study of syphilis-like bone changes in nonsyphilitic infants led to the discovery of this new entity. In bone syphilis there are scattered areas of cortical destruction and even metaphyseal changes. Negative serologic tests in the infant and parents help to rule out syphilis. Fig. 4 shows subperiosteal new bone formation easily mistaken for congenital syphilis. Bone destruction is not present.

Hypervitaminosis A is occurring more frequently, usually as a result of administering a concentrated preparation in teaspoonful doses rather than by drops. There are hyperirritability and hyperostosis present. The differentiation from infantile cortical hyperostosis is easy. Its onset is later (after six to twelve months), there is little or no fever, and the blood vitamin A concentration is high. Furthermore, there is a history of excessive vitamin A intake and rapid recovery after halting vitamin A administration.

Trauma: Subperiosteal hematomas following trauma are rarely multiple, and the overlying skin is commonly discolored.

Scurvy has to be considered in the differential diagnosis. It produces periosteal elevation and similar subperiosteal calcification which, however, extends to the end of the metaphysis. There is associated a narrow accentuated pencil-line zone of provisional calcification, with fragmented borders at the metaphysis and decreased density of the secondary epiphysis. Vitamin C therapy produces immediate clinical improvement. A history of adequate vitamin C intake will easily rule out scurvy.

Malignant neoplasm of bone is extremely rare in infants. Its lesions are locally destructive and solitary. In bone metastasis from neuroblastoma the x-ray usually shows destruction of cortex adjacent to the epiphysis and a motheaten appearance, not unlike disseminated osteomyelitis. It is important to rule out bone malignancy because there are reports of cases of infantile cortical hyperostosis in which sarcoma was diagnosed and radical operation recommended. In

Fig. 4.—Involvement of ribs, pelvic bones, and long bones. Case 3.

leukemia the findings in the blood and bone marrow will reveal the diagnosis.

THERAPY

There is no specific therapy. Treatment is symptomatic. Due to the hyperirritability, sedation is frequently necessary. Supportive measures such as supplementary vitamins and iron medication for the associated anemia are given. In severe cases transfusions are helpful. Hormonal therapy (ACTH and cortisone) has been tried since its recommendation by Bush and Merrell[36] in 1952. It was believed that hormone therapy involves dangers warranting a stringent attitude toward administration in such a benign disease. However, the occurrence of severe cases of infantile cortical hyperostosis which lead to lasting deformity and crippling warrants the use of cortisone under carefully supervised and controlled conditions. We have given cortisone to two of our patients and have the impression that it controlled the symptoms well and shortened the course of the illness.

CASE REPORTS

CASE. 1.—S. L. W. (No. 26243), a 3-month-old Negro male, was well until three weeks prior to admission. At that time the child began to be fretful and quite irritable. Three days prior to admission the child's eyes became swollen and had a yellow purulent discharge. The mother also noticed that the jaws were swollen and that he cried when the cheeks were touched. The child had felt feverish during the entire illness. On admission the temperature was 101° F. The patient was a well-developed, well-nourished Negro male, who was quite irritable. Erythema and swelling were present over both cheeks, which were very tender to touch. There were periorbital edema and conjunctivitis, with purulent discharge from the eyes. Moderate nuchal rigidity was present, but no adenopathy.

Laboratory Findings.—Lumbar puncture was negative; urinalysis, negative; hemoglobin, 9.3 grams per cent; red blood cells 3.74 million; white blood count 11,950; 46 segmented forms, 13 band forms; 44 lymphocytes; 6 monocytes; 1 eosinophil. Mantoux 1:1,000 was negative; Kline test, negative. Sickle-cell preparation was negative. Serum calcium 10.2 mg. per cent; serum phosphorus 5.0 mg. per cent; serum phosphatase 6.2 Bodansky units. Sedimentation rate was 64 mm. per hour.

X-rays.—Films on May 27, 1954, "show subperiosteal new bone formation of the mandible, especially each ramus. No other abnormality involving the visualized bones or joints can be seen." On June 9, 1954, "films of the mandible and long bones, as well as posteroanterior and lateral films of the chest, show a thick layer of infantile cortical hyperostosis over the mandible and probably some involving both clavicles. The mid-ribs, laterally, also show some definite subperiosteal new bone formation." On June 22, 1954, Fig. 2, "the new bone of the mandible is quite dense and more symmetrical as well as that of the clavicles, especially in the midportion. The several ribs, previously seen to be involved, show thick periosteal new bone formation." The last films, on July 25, 1954, show, "slight but definite progression of new bone formation about the mandible and clavicles. The involved ribs appear essentially unchanged."

The patient was febrile and irritable for two weeks after admission. Then he had a spontaneous remission but relapsed, at which time the clavicles and ribs became involved. He was then put on cortisone (12½ mg. b.i.d.) to which he showed a definite clinical response. The cortisone was slowly withdrawn and the child was watched in the hospital for another week. He was discharged improved after six weeks' hospitalization.

CASE 2.—W. L. Y. (No. 1083), a 5-month-old white male, was admitted to Bradford Hospital on July 1, 1949. The patient was in good health until two months before admission, when the mother noted that there was a swelling on the right side of the face, in the cheek area, which became progressively larger. Three weeks before admission there was a similar swelling in the left side of the face. The right-sided swelling had increased progressively and had remained very tender.

On admission there was a firm soft tissue swelling in the right parotid area, extending below the angle of the jaw. It seemed very tender and warm. There was a much smaller swelling in the left parotid area.

The differential diagnosis was: parotitis, parotid tumor or stone in the parotid duct.

X-ray examination of the mandible to include the skull and the upper portion of the thorax showed a definite hyperostosis, involving the right side of the mandible; the left side appeared to be entirely normal. The clavicles, scapulas, and the chest also appeared to be normal. The diagnosis was Caffey's disease, and the child was discharged improved after one week.

CASE 3.—N. E. (No. 1435), a white female, 2½ months of age, was admitted to Bradford Memorial Hospital on March 24, 1949, because of her inability to cry and to take her feedings normally.

Physical examination revealed definite microcephaly. The only other positive finding was bowing of the tibia and prominence of the internal malleolus. Spinal fluid and blood Wassermann tests were negative. Serum phosphorus was 4.8 mg. per cent, serum calcium 9.5 mg. per cent, and serum phosphatase 5.4 Bodansky units. Fig. 4, a film of the long bones, together with films of the chest and abdomen, shows subperiosteal new bone formation of most of the long bones. At first examination this has the appearance of congenital syphilis. However, with the widespread distribution and especially involvement of the ribs and with absence of clinical and serologic proof of congenital syphilis, a diagnosis of infantile cortical hyperostosis was considered. A review of the films of the skull showed the mandibles to be normal. The child was discharged unimproved after eight days' hospitalization.

CASE 4.—C. L. B. (No. 12896), a 5-month-old white male, was admitted to Bradford Hospital, on Jan. 7, 1952, with the history of swelling of the face for five days, which had gradually progressed.

On admission the face showed an asymmetric indurated area over the right zygoma. There was no cellulitis. The mouth could be opened without difficulty. The first impression was osteomyelitis of the maxilla. The child was put on sulfadiazine and penicillin. The Wassermann was negative.

X-ray films of the long bones, chest, and skull and oblique films of the mandible showed definite hyperostosis, involving both sides of the mandible. This had the characteristic appearance of Caffey's disease. There was no suggestion of abnormality involving the shoulder girdles, the ribs, or any of the long bones.

The patient stayed in the hospital one week. The swelling slowly subsided and the face was symmetrical on discharge.

CASE 5.—E. R. M. (No. 97289), a 6-month-old Negro male, was admitted to Parkland Hospital with the history of low-grade fever and marked irritability for five to six days. About one month prior to admission the patient had a low-grade fever and a swelling on the right hand, which seemed painful. At that time he was taken to Freeman Clinic, where x-ray films showed no abnormality. The swelling subsided, and the patient did well, until five days prior to admission, when both feet became swollen to the level of the ankles. This subsided within a

few days spontaneously. One day before admission the patient developed a swelling of his arms and hands.

On admission the temperature was 101.2° F., the child was quite irritable, especially when moved. There was a brawny tender swelling of the right hand and right forearm and the left hand.

Laboratory Findings.—Sickle-cell preparation, Wassermann and Kline tests were negative; urinalysis negative. White blood count was 20,300; band forms 5; segmented forms 69; and lymphocytes 26. Fasting ascorbic acid level was 15 mg. per cent. Total serum protein was 6.9 grams; blood culture negative; sedimentation rate 9 mm. per hour. The impressions were: (1) scurvy, (2) osteomyelitis, (3) syphilis.

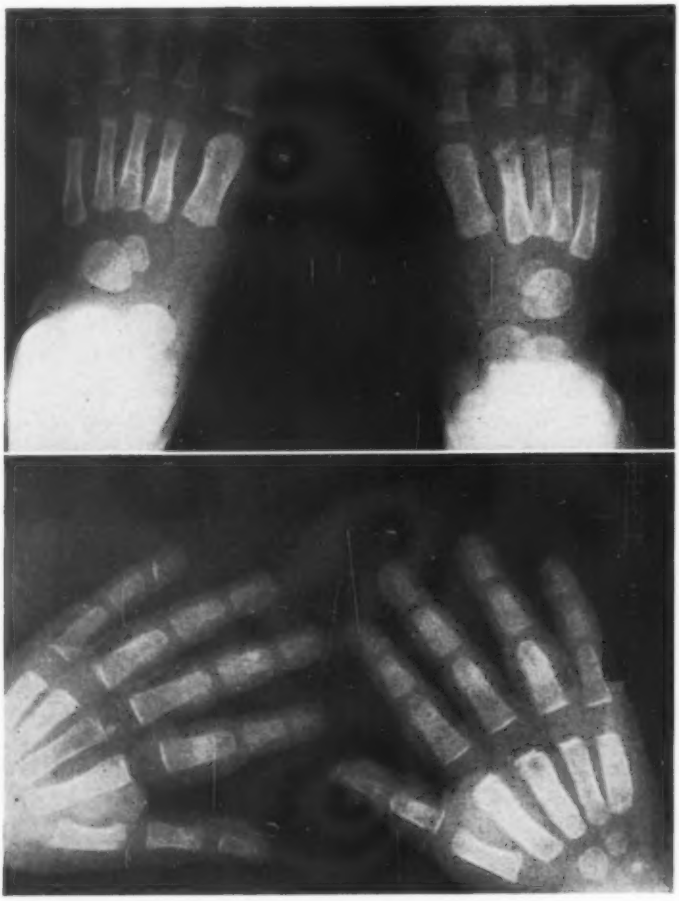

Fig. 5.—Metatarsal and metacarpal involvement. Case 5.

Radiographs of the long bones showed cortical thickening of the second metatarsal on the left foot, third metatarsal on the right foot, and third metacarpal of the right and left hands, with suspected early involvement of the other metacarpal and metatarsal bones (Fig. 5). There also seemed to be early bilateral involve-

ment of the ulnas, more marked on the left, where cortical thickening was suspected. This was also true of the humerus and of the femurs. The mandible was not involved. The findings are compatible with infantile cortical hyperostosis.

The course in the hospital was uneventful, the swelling subsided without any specific treatment. The temperature became normal, and the child was sent home after two weeks.

CASE 6.—M. D. H. (No. 110788). A 4-month-old Negro male infant, was admitted to Parkland Hospital on April 6, 1954, with a history of fever and cough for fifteen days and vomiting and diarrhea for three days. Swelling of the right jaw and periorbital region and pain on movement of the arms were noticed for two weeks. There was no history of trauma. The family history was negative.

The temperature was 100° F. and the weight was 14 pounds 6 ounces. The physical examination showed edema of the right submandibular area and swelling and tenderness of the right upper extremity. There was marked pain on passive motion of arms and legs and on palpation of the mandible.

Laboratory Findings.—Hemoglobin was 10.6 grams per cent; white blood count 14,800; differential normal. Urinalysis was negative, blood culture negative; Wassermann negative; Kline negative; sickle-cell preparation negative. Blood calcium was 11.4 mg. per cent; phosphorus 6.9 mg. per cent.

The clinical impressions were: (1) congenital syphilis, (2) Caffey's disease, (3) trauma, (4) scurvy, (5) sicklemia, (6) infectious periostitis.

Films of the mandible showed considerable subperiosteal new bone formation, involving the right ramus and body of the mandible and a similar change, barely noticeable, over the left ramus of the mandible. Both ulnas showed also the same type of periosteal reaction, representing hyperostosis involving almost the entire shaft of the ulna, on either side. This reaction progressed over a period of time and left little doubt that these were the changes of infantile cortical hyperostosis.

The infant stayed in the hospital for eight days. He continued to have fever and pain on motion of the arms but was discharged because his family was moving to Louisiana.

CASE 7.—La. Me. C. (No. WW 755). On June 1, 1948, a 4-month-old, undernourished and underdeveloped, white female weighing 11 pounds 5 ounces, was referred to Freeman Clinic by a physician in Bangs, Texas, who had diagnosed rickets. He noticed no change in the baby's condition after antirachitic treatment. The mother gave the history that the child had not gained weight adequately, that she seemed not to use her arms properly, and that the shoulder blades appeared to be swollen. The swelling of the shoulders became gradually worse and the infant would scream when touched. About this time the face became swollen and this swelling had persisted.

Physical examination revealed a quite irritable, underdeveloped child. Both sides of the face were slightly swollen, the right more than the left. The suprascapular areas were swollen bilaterally and the infrascapular muscles seemed hypertrophic.

Laboratory Findings.—Hemoglobin was 11.9 grams per cent; white blood cells 14,600; 31 polymorphonuclears; 65 lymphocytes; 1 monocyte; 3 eosinophils. Wassermann and Eagle flocculation tests were negative.

X-ray Reports.—Films of the long bones, together with a film of the chest, showed a peculiar increase in density in both scapulas. These bones appeared considerably thickened, apparently due to the increment of the cortex. There was no involvement in any of the other visualized bones. The mandibles were well demonstrated and there was no definite thickening of the cortex or of its periosteum (Fig. 6).

The conclusion was infantile cortical hyperostosis of the scapulas. After the diagnosis was made the child was referred back to her physician.

CASE 8.—R. L. C. (No. 25316), a 3-month-old white male, had been a patient at Bradford Memorial Hospital at 1 month of age, with a diagnosis of congenital malformation of the epiglottis, hypothyroidism, and hereditary abnormality of the eyes.

The present illness began one week prior to admission, at which time the baby became highly irritable and his left jaw began to swell. After a few days the right side of the jaw was also swollen. The mass on the left jaw was found to be tender but not hot to touch. Penicillin and streptomycin and hot pads were ordered. Five days later there was no improvement and the child was hospitalized.

The patient was a fairly well-developed, irritable white male. The temperature was 102° F. There was bilateral swelling over the lateral portion of the mandible and maxilla, giving the appearance of "someone trying to blow a horn." This tumor-like mass was larger on the left than on the right side, and though not hot to touch, was quite tender. There was no fluctuation on palpation.

Laboratory Findings.—Hemoglobin was 9.9 grams per cent; red blood cells 3,860,000; white blood cells 16,000; 57 adult polymorphonuclears; 10 bands, 31 lymphocytes; 1 monocyte; 1 eosinophil; urinalysis negative, serum calcium 9.5 mg. per cent; serum phosphorus 5.2 mg. per cent; serum phosphatase 5.3 Bodansky units. Corrected sedimentation rate was 38 mm. per hour.

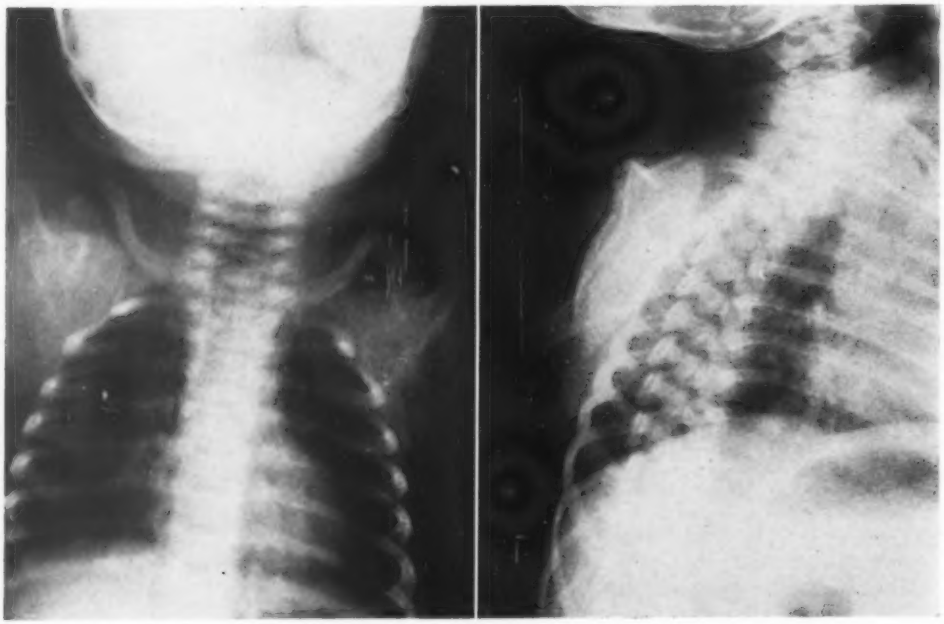

Fig. 6.—Infantile cortical hyperostosis with bilateral scapular involvement. Case 7.

X-ray Studies.—June 23, 1954. Films of the skull, to include the mandible and films of the long bones, showed the typical appearance of infantile cortical hyperostosis, involving the mandible, especially on its left side. It was also noted that there was a sub-

periosteal reaction along the medial aspect of each humerus. These were considered to be the changes of Caffey's disease. The other bones appeared to be intact.

X-rays taken July 2, 1954, showed some new subperiosteal bone formation on the inferior margin of some of the ribs, especially on the right, principally the fifth, sixth, and seventh. There was minimal if any evidence at this time of any involvement of the humeri, clavicles, or scapulas.

b.i.d., then to 12½ mg., and then 6¼ mg. once daily. No adverse effects were noted at any time. The child was discharged improved after one month.

CASE 9.—L. L. R. (No. 4286), a 4-month-old white male, was admitted to Bradford Memorial Hospital on March 7, 1950, with the chief complaint of swelling of the cheeks for the past two weeks, swelling of the neck, and refusal to nurse for two

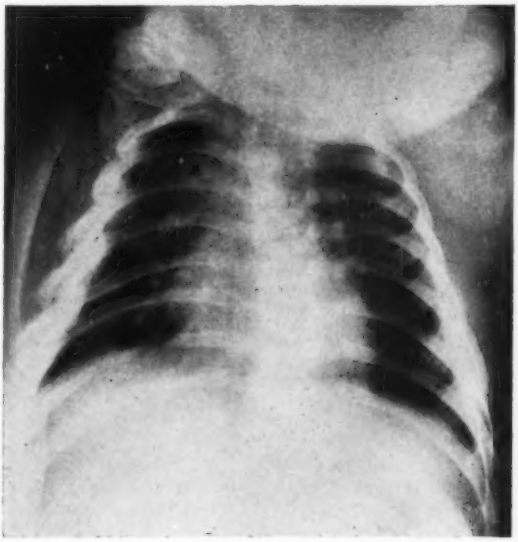

Fig. 7.—Bilateral scapular and rib involvement. Case 9.

X-rays on July 15, 1954, showed excellent demonstration of subperiosteal new bone formation of the mandible of Caffey's disease.

The child was placed on procaine penicillin and streptomycin. He was afebrile after several days and remained so through his hospitalization. Cortisone was given, 12½ mg. t.i.d., besides a low salt diet and added potassium. The child tolerated this treatment very well. The swelling in the child's mandible gradually decreased in size, and finally the area became nonpainful to pressure. Toward the end of the hospital stay, cortisone was diminished to 12½ mg.

days. One month prior to admission the patient developed fever, which was diagnosed as bronchopneumonia. He responded well to treatment, but several days later again began to run fever, which continued to the time of admission.

Physical Examination.—Examination revealed a poorly nourished, poorly developed, white male. Temperature was 101° F. rectally. The face was greatly enlarged, compared to the head, because of semifirm, nonpitting edema of the cheeks, extending downward over the inferior border of the mandibles into the neck. Over the left sternoclavicular junction there

was a firm, tender, nonmovable mass about 2 by 2 cm. in diameter, which appeared to be an enlarged medial end of the clavicle.

Laboratory Findings.—Hemoglobin was 9.6 grams per cent; red blood count 3,590,000; white blood count 29,000, with a shift to the left. Wassermann test was negative; serum calcium 11 mg. per cent; phosphorus 5.98 mg. per cent; phosphatase 11.5 Bodansky units.

X-ray Studies.—Film of the mandible taken on March 7, 1950, showed an excellent visualization of the increment of new bone around the mandible. There was also evidence of involvement of the clavicles and the fifth rib on the right laterally. The scapulas were apparently intact. Film of the chest on March 27, 1950, showed considerable hyperostosis of the left scapula. This apparently had developed within the three-week period. On the right there also was evidence of swelling and a peculiar mass above the right scapula. In addition, both midportions of the humerus were also thickened. Most of the ribs, especially those on the right lateral chest wall, showed considerable hyperostosis (Fig. 7).

Hospital Course.—The patient was hospitalized for twenty-three days, during which he received penicillin for thirteen days and dihydrosteptomycin for eight days, with little if any change in the course except a mild decrease in the size of the cheeks, neck, and left clavicle. Several blood transfusions were given in an effort to ascertain if blood would help this condition. The febrile course continued, and the patient was tried on Aureomycin, during which time he developed enlargement of the left scapula and both wrists. Because it was evident that the drugs were not going to be of great value, the patient was discharged to be followed in the clinic.

The following case demonstrates the importance of suspecting infantile cortical hyperostosis whenever there are fever, irritability, and swelling of the face in an infant. During a week's hospitalization, the case was not diagnosed clinically or roentgenologically. A review of the films one month later revealed the diagnosis.

CASE 10.—D. F. L. (No. 6753), a 4-month-old white female infant, was admitted to Bradford Memorial Hospital on Aug. 7, 1950, with the chief complaint of swelling of the face below both eyes for two days, and a low-grade fever. Three and a half weeks before she began to be fretful, refused to take the bottle, and would cry when picked up. The parents noted that she was not turning her head. X-rays of her cervical spine made at that time were negative and the blood count revealed 18,000 white cells.

Physical Examination.—Examination revealed a well-developed child, weighing 11 pounds 8 ounces, lying quietly in bed. There was a slight swelling and redness below both eyes. The face was enlarged on the right side; the right maxilla seemed to protrude forward more than the left maxilla.

Laboratory Findings.—Hemoglobin was 9 grams per cent; red blood cells 3,900,000; white blood cells 20,600; adult polymorphonuclears 48; immature polymorphonuclears 8; lymphocytes 30; monocytes 13; eosinophils 1. All other laboratory findings, including blood culture, spinal puncture, and bone marrow studies, were negative. White blood count on August 12 was 19,250, and on August 15, 20,900, with left shift.

X-ray Studies.—Posteroanterior and lateral films of the chest showed no abnormality involving the lung parenchyma or the various visualized bones. The following day films of the facial bones, as well as of the cervical vertebrae, were obtained and showed no abnormality of the cervical vertebrae, but a suspicion of retropharyngeal inflammation was suggested. On these films the periosteal thickening of the mandible was quite well visualized

and appeared to be typically that of infantile cortical hyperostosis. This finding was not described on the original report.

Hospital Course.—The patient was running a low-grade fever from 100° to 101° F. during the course of hospitalization. An ear, nose, and throat consultant thought of an allergic condition as the cause of the swelling. The patient was given penicillin with the idea that there were some signs of infection present. The edema and discoloration improved somewhat, but the infant was still irritable and had a low-grade fever when she was discharged, undiagnosed, after eight days.

Films of the thorax and abdomen, as well as of the long bones, made about a month later, showed extensive involvement of both bones in the forearms and the legs (Fig. 8). In addition, several ribs showed the typical thickening of the periosteum, as well as involvement of both clavicles. The scapulas appeared to be intact.

The following case proves that the diagnosis of infantile cortical hyperostosis is easy if the physician is familiar with the symptoms and signs of this disease:

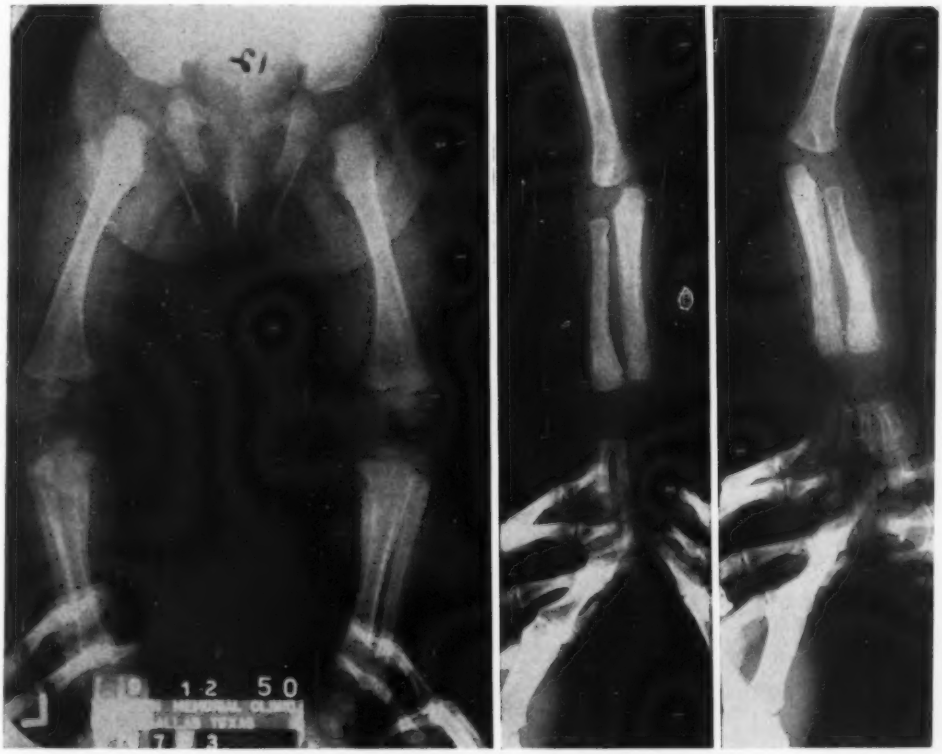

Fig. 8.—Subperiosteal new bone formation usually called congenital syphilis. Case 10.

Case 11.—H. B. (No. 31868), a 4-month-old Negro male infant, became ill fourteen days prior to admission, with irritability, fever, vomiting, and diarrhea. The vomiting and diarrhea cleared after two days, but fever and irritability continued. Ten days before admission the left jaw and five

days later the right jaw became swollen and tender to touch. The attending physician found 15,650 white blood cells, and did a spinal puncture which was traumatic. The patient was referred to a pediatrician who treated him for six days at a local hospital as a possible case of brain abscess with penicillin, Chloromycetin, and streptomycin. X-ray films of the skull made by a radiologist were thought to be negative. Because there was no change in the condition, the baby was transferred to Children's Medical Center in Dallas on June 22, 1955, for diagnosis and treatment.

Physical Examination.—Examination revealed a pale infant who held the neck in hyperextension to prevent the jaws from touching the chest. Temperature was 102° F. There were marked swelling of the soft tissues about the mandible and intense mandibular tenderness. The admitting resident pediatrician made the diagnosis of Caffey's disease after examining the child and reading the x-ray films which the mother brought along.

Laboratory Findings.—White blood count was 18,050, with 35 polymorphonuclears, 2 bands, 58 lymphocytes, 4 monocytes, 1 eosinophil. Hemoglobin was 8.75 grams per cent, C-reactive protein 2 plus, Kline test negative, sickle-cell preparation negative, bone marrow studies negative. Urine was negative; serum calcium 11.2 mg. per cent; serum phosphorus 5.28 mg. per cent; serum phosphatase 13.6 Bodansky units. Blood culture was negative.

X-ray Studies.—Films demonstrated again the subperiosteal new bone formation about the ramus of both mandibles. There were no other similar changes in the scapulas, clavicles, ribs, or bones of the extremities. The child was treated with penicillin and iron medication. He continued to have a temperature of 101° to 102° F. for seven days. Within the following ten days the temperature gradually returned to normal. The mandibular tenderness disappeared, and only a slight swelling remained bilaterally. The child was discharged in good condition after twenty-one days.

SUMMARY

A description of the clinical picture, laboratory findings, differential diagnosis, etiology, therapy, and prognosis of infantile cortical hyperostosis, with a review of the literature, is presented.

Eleven new cases of infantile cortical hyperostosis are reported.

Four of this series occurred in Negro infants.

Bilateral scapular involvement was found in two cases.

Infantile cortical hyperostosis is not a rare entity and should be suspected in every infant with fever, leukocytosis, hyperirritability, and swelling of the soft tissues. The diagnosis is established by x-ray studies of the underlying bones.

We are indebted to Dr. Edward L. Pratt, Professor of Pediatrics, for assistance in preparing this paper.

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A NEW QUANTITATIVE APPROACH TO THE STUDY OF ANTHELMINTHIC DRUGS, WITH AN EVALUATION OF PIPERAZINE HEXAHYDRATE, PHTHALYLSULFATHIAZOLE, AND RO 2-5655/3* IN THE TREATMENT OF ENTEROBIUS INFECTION

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NO UNIFORMITY of opinion exists regarding an effective therapeutic agent for the treatment and control of *Enterobius vermicularis*. Many drugs have been recommended in the literature. However, some have intrinsic defects and inadequacies which prevent them from meeting the requirements for satisfactory therapy and others have not yet been properly evaluated. The present investigation was designed to fill some of the gaps existing in the literature by evaluating the effectiveness of three drugs in the therapy against enterobiasis in man, and by suggesting a method for the quantitative determination of the intensity of infection before and after treatment.

MATERIALS AND METHODS

All of the persons treated for Enterobius infections were residents of a mental institution, the Florida Farm Colony, Gainesville, Florida. The patients were housed in buildings of between thirty and forty beds. All the patients in each of eight buildings were investigated. The residents of six buildings received the three experimental drugs and the residents of two buildings were left untreated, as controls, with the recognition that over a period of time some individuals may become negative without treatment. The patients in each building received the same drug for the same length of time. By treating the entire population in each building we hoped to minimize the possibility of reinfection, of contamination of the samples to be examined, and of errors on the part of the nurse in giving the medication and in collecting the specimens.

Cellulose tape slide preparations were used to collect specimens for evidence of Enterobius infection. Preparation and use of the slides were essentially by the technique described by Brooke and co-workers.[1] Only one nurse collected specimens, taking them at night between 9 o'clock and midnight. She washed her hands thoroughly at regular intervals in order to minimize the danger of transferring eggs from tape to tape by contaminated fingers.

In the laboratory, a drop of toluene was placed under the tape and examination was made with a 16 mm. objective and a 5X ocular.[2] The entire slide was examined, requiring ten to fifteen minutes. This time was greater

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*The use of these drugs does not constitute approval or endorsement by the Public Health Service.

than that required to examine only the portion of the tape that touched the patient's body, as recommended by previous authors. However, preliminary observations indicated that for a significant number of patients only a few eggs in a marginal position were present which might be missed if only a portion of the tape was examined.

Before therapy was begun, the patients were examined daily for six consecutive days. Previous results[3] indicate that at least three consecutive examinations are necessary to reveal a fairly constant proportion of the infections observed in populations with different prevalence rates. In evaluating the relative effectiveness of the drugs, another series of six daily consecutive examinations was made, beginning one week after the termination of therapy. This interval of time following therapy was selected in order to preclude the possibility of reinfection since, according to Cram,[4] approximately fifteen to twenty-eight days are required for the completion of the life cycle of *E. vermicularis*.

From the beginning of this study it was realized that the number of individuals who become worm-free is not the only criterion of effectiveness of a therapeutic program. There have been conflicting reports concerning the anthelminthic activity of various drugs against *E. vermicularis*, primarily because various workers have paid little attention to comparison of the worm burden before and after treatment. In the present work an attempt has been made to obviate these shortcomings by an indirect quantitative determination of the intensity of the infection. With most helminthic infections this can be done by counting the number of eggs found in the feces. The number of Enterobius eggs found in the cellulose tape preparation, however, would obviously have little relationship to the number of worms harbored by a patient, since many variables, such as the peculiar egg-laying habits of the female worms, the time and method of collection, the hygienic habits of the patient, the amount of scratching he does, and various other factors will modify the number of eggs which are picked up by the cellulose tape. However, in view of the fact that egg deposition in the perianal region apparently does not take place every day,[5] it is believed that the greater the number of worms harbored by a patient, the greater the chances that eggs will be found on the day of collection. Thus, if six consecutive daily specimens are positive in one individual, it can be assumed that the worm burden is higher than if only one or two specimens were positive and the rest were negative. In a given population group, a relative measure of the average intensity of infection can thus be determined by a summation of the product obtained by multiplying the percentage of individuals having positive specimens on no occasion, once, twice, and in progression up to six times by the corresponding factors 0, 1, 2, 3, 4, 5, or 6. The figure thus obtained has been named the coefficient of infection (C.I.) and used for the sake of comparison of the relative intensity of infection in different population groups.

In conference with a consulting physician,* three drugs were selected for testing, piperazine hexahydrate, phthalylsulfathiazole, and RO 2-5655/3 (m-allyloxyphenylear-bamy methyl dipropy [p-chlorobenzyl] a m m o n i u m

*Dr. Harry Most, M.D., CDC Consultant.

chloride monohydrate), and were made available free to the institutions by three pharmaceutical companies. The attending physician (C. H. C.) examined each patient, and dosage was determined according to the weight of the individual. During administration of the drugs, the patients were under the careful supervision of the physician and the nurse in attendance in order to detect any toxic reaction resulting from the therapy. Two levels of drugs were administered, one designated as a low dose given for seven consecutive days, the other as a high dose given for fourteen consecutive days. Piperazine hexahydrate was given in the form of a palatable 10 per cent syrup containing 100 mg. per milliliter of syrup; phthalylsulfathiazole was given in an oral suspension containing 1 Gm. of active ingredient per 5 ml. of syrup; and RO 2-5655/3 was administered in the form of 200 mg. tablets. The daily dosages are summarized in Table I.

No obvious toxic symptoms were observed in any of the patients treated with piperazine hexahydrate or phthalylsulfathiazole in either dosage. On the other hand, disagreeable reactions to the RO 2-5655/3 were observed in a number of patients receiving this drug, the following symptoms being noted: diarrhea, nineteen cases; vomiting, ten cases; vomiting, diarrhea, headache, and dizziness in one case. Medication was discontinued in the latter patient after four days.

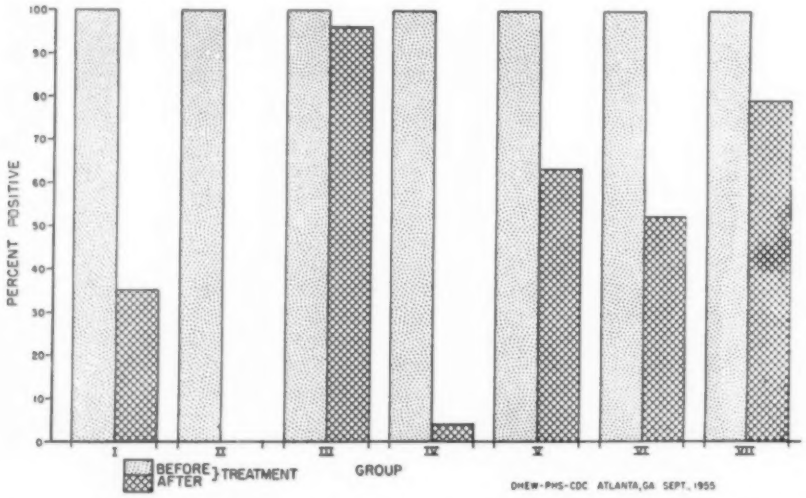

Fig. 1.—A comparison of per cent infection with *E. vermicularis* before and after treatment.

Examination of all the cellulose tape preparations could not be completed before the administration of therapy. Therefore, selection of wards on the basis of prevalence and intensity of infection was not possible.

RESULTS AND DISCUSSION

Pretreatment examination in the eight wards included in this experiment revealed that 200 of 265 patients (75 per cent) were infected with *E.*

TABLE I. THE EFFECT OF THERAPY ON THE PER CENT OF INFECTION WITH E. VERMICULARIS

GROUP NUMBER	PERSONS IN GROUP	NUMBER INFECTED	PREVALENCE PER CENT	DRUG	DOSAGE, PER DAY	DURATION OF THERAPY IN DAYS	RESULTS OF TREATMENT AMONG INFECTED INDIVIDUALS	
							NUMBER WHO BECAME NEGATIVE	PER CENT WHO BECAME NEGATIVE
I	39	20	51	Piperazine hexahydrate	2 Gm.	7	13	65
II	36	24	67	Piperazine hexahydrate	Under 20 kg., 2 Gm. 20 to 29 kg., 3 Gm. 30 to 39 kg., 4 Gm. 40 kg. and over, 5 Gm.	14	24	100
III	25	24	96	Phthalylsulfathiazole	8 Gm.	7	1	4
IV	33	25	76	Phthalylsulfathiazole	Under 20 kg., 12 Gm. 20 kg. and over, 16 Gm.	14	24	96
V	39	38	97	RO 2-5655/3	2 Gm.	7	14	37
VI	33	27	82	RO 2-5655/3	Under 20 kg., 1.0 Gm. 20 to 29 kg., 1.5 Gm. 30 kg. and over, 2.0 Gm.	14	13	48
VII	60	42	70	None	-	-	9	21

TABLE II. THE EFFECT OF THERAPY ON THE INTENSITY OF INFECTION WITH E. VERMICULARIS

GROUP NUMBER	POSITIVES IN GROUP	PER CENT OF PERSONS WITH N POSITIVE SPECIMENS BEFORE TREATMENT						COEFF. OF INFEC.	PER CENT OF PERSONS WITH N POSITIVE SPECIMENS AFTER TREATMENT							COEFF. OF INFEC.
		N = 1	N = 2	N = 3	N = 4	N = 5	N = 6		N = 0	N = 1	N = 2	N = 3	N = 4	N = 5	N = 6	
I	20	30	25	15	20	5	5	260	65	20	0	5	5	0	5	85
II	24	54	17	13	8	4	4	203	100	0	0	0	0	0	0	0
III	24	21	8	8	17	4	42	401	4	21	13	8	8	25	21	354
IV	25	28	36	20	12	4	0	228	96	0	0	4	0	0	0	12
V	38	21	16	18	16	8	21	337	37	29	18	3	5	3	5	139
VI	27	30	30	11	22	7	0	246	48	30	7	7	0	4	4	109
VII	42	35	23	17	10	10	5	252	21	12	12	12	14	12	17	290

vermicularis. The prevalence rate varied from 51 per cent in one building to 97 per cent in another. No correlation of the prevalence rate with the race and sex of the patients was observed.

The results of the effect of therapy on the per cent of infection are summarized in Table I and presented graphically in Fig. 1.

Piperazine Hexahydrate.—Sixty-five per cent of twenty infected individuals became negative after receiving 2 Gm. of this drug daily for seven days (Group I). When treatment was given for fourteen days in higher doses 100 per cent of twenty-four became negative (Group II).

While piperazine has been used in the past for various purposes, its effectiveness against *E. vermicularis* has only recently been established. White and Standen[6] and Bumbalo and associates[7] administered this drug for seven consecutive days, followed by seven days without medication, after which a second course of seven days of therapy was given. Brown and Chan[8] found that a single course of treatment for fourteen consecutive days was more effective. Essentially similar results were reported by Ricci and Corbo.[9]

Phthalylsulfathiazole.—Whereas only 4 per cent of twenty-four infected individuals became negative following a seven-day course with 8 Gm. daily (Group III), 96 per cent of twenty-five became negative as a result of heavier doses for fourteen consecutive days (Group IV).

Askue and Tufts[10] reported moderate success with this drug and concluded that it is not as effective against *E. vermicularis* as gentian violet.

RO 2-5655/3.—Thirty-seven per cent of thirty-eight individuals became negative after treatment for seven consecutive days with 2 Gm. daily (Group V), whereas 48 per cent of twenty-seven became negative when treated for fourteen consecutive days with somewhat lower doses. Higher dosages could not be tested in view of the toxic manifestations frequently encountered with this drug.

This drug has shown anthelminthic activity against *Syphacia obvelata*, the pinworm of mice,[11] and has given encouraging results when used in children at a level of 20 mg. per kilogram of body weight.[12]

Untreated Controls.—Twenty-one per cent of forty-two individuals infected had become negative at the end of the experiment. The chief point of interest to be observed in this group is that if treatment with a wholly ineffective drug had been instituted, apparent cures (on the basis of the criteria used in testing various therapeutic agents) would have resulted in nine instances. The results from the untreated group, in terms of per cent of infection, were not very dissimilar from those obtained with the low dose of phthalylsulfathiazole or with RO 2-5655/3.

The results of the effect of therapy on the intensity of infection are summarized in Table II and presented graphically in Fig. 2. The coefficient of infection before treatment varied from 203 (Group II) to 401 (Group III). A certain correlation between the prevalence of infection in each group and the intensity of infection as determined by the C.I. is apparent. The low dose of piperazine hexahydrate brought a reduction in the C.I. from 260 to 85 (Group I), where-

as the high dose brought about a reduction from 203 to 0 (Group II). With phthalylsulfathiazole, the low dose produced a reduction of the C.I. from 401 to 354 (Group III), whereas the high dose produced a reduction from 228 to 12 (Group IV). RO 2-5655/3 was somewhat effective, although less than the above medications in bringing about a reduction of the C.I. The reduction was approximately the same whether the drug was brought to light. Whereas a reduction in the per cent of infection was observed among the untreated controls, the opposite was true with regard to the intensity of infection (Group VII). By comparing the results on the persons treated with a low dose of phthalylsulfathiazole (Group III) or with RO 2-5655/3 (Group V and VI) with their controls (Group VII) the anthelminthic activity of these drugs is not apparent on the basis of

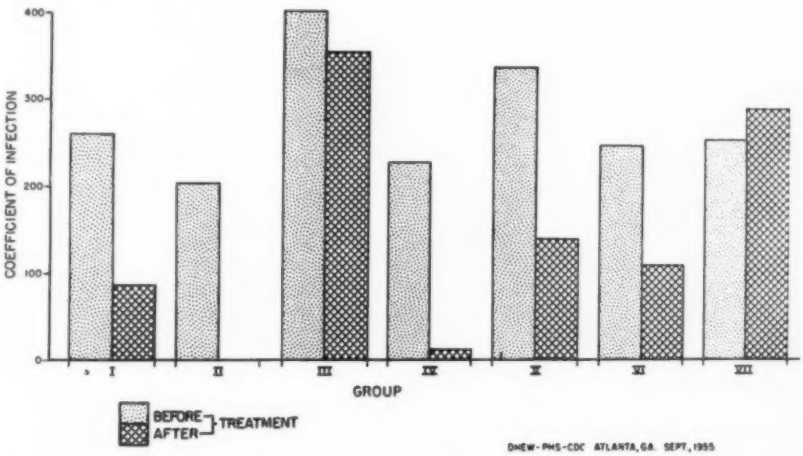

Fig. 2.—A comparison of the intensity of infection with *E. vermicularis* before and after treatment as measured by the coefficient of infection.

administered for seven days (Group V) or for fourteen days (Group VI).

No reduction in the intensity of infection was observed in the untreated control group during the period in which the therapeutic trial was conducted (Group VII). Actually, in the control wards, the C.I. changed from 252 to 290 during the period of observation.

By comparing the results obtained on the per cent infection with those on the intensity of infection (Figs. 1 and 2) several significant facts are the per cent reduction of infection (Fig. 1), whereas it is evident on the basis of the reduction of the worm burden (Fig. 2). If only the changes from positives to negatives are considered (Fig. 1), the experimental setup appears to be evenly arranged. Actually, when the C.I. is considered, some irregularities existed among the groups subjected to treatment. As indicated in Fig. 2, the persons treated with low dose of piperazine hexahydrate (Group I) had, on the average, a much lower intensity of infec-

tion than those treated with the low dose of phthalylsulfathiazole (Group III). Although less obviously so, the same relationship existed among those receiving low doses with the various drugs (Groups I, III, and V) and those receiving high doses (Groups II, IV, and VI). In other words, piperazine hexahydrate was not submitted to such a severe test as phthalylsulfathiazole and RO 2-5655/3, and all the three drugs in high doses were not submitted to such a severe test as in the low doses.

indicated in Table III, of the ninety-eight persons who had become negative during the period in which the therapeutic trial was conducted, 40 per cent had been found positive once and only 1 per cent on six examinations. The C.I. for this group was 227. On the other hand, of the 102 patients who remained positive following therapy (failures), 19 per cent had been found positive once and 24 per cent on six examinations. The C.I. in this group was 350. These results are in agreement with and ex-

TABLE III. A COMPARISON OF THE INTENSITY OF INFECTION OF PATIENTS WHO BECAME NEGATIVE DURING THE TIME OF THE THERAPEUTIC TRIAL AND THOSE WHO REMAINED POSITIVE

RESULTS AFTER THERAPEUTIC TRIAL	NUMBER	PER CENT WITH N POSITIVE SPECIMENS BEFORE TREATMENT						COEFFICIENT OF INFECTION
		N = 1	N = 2	N = 3	N = 4	N = 5	N = 6	
Negative	98	40	23	13	19	4	1	227
Positive	102	19	21	16	13	7	24	350

TABLE IV. THE PREVALENCE AND INTENSITY OF INFECTION AMONG PATIENTS RE-EXAMINED 67 DAYS AFTER THERAPY

GROUP NUMBER	EXAMINATION BEFORE THERAPY	PATIENTS RE-EXAMINED 67 DAYS AFTER THERAPY			COEFFICIENT OF INFECTION	
		NUMBER IN GROUP*	NUMBER POSITIVE	PER CENT POSITIVE	BEFORE THERAPY	67 DAYS AFTER THERAPY
II A	Positive	20	4	20	203	65
II B	Negative	10	3	30	0	90
IV A	Positive	24	5	21	337	33
IV B	Negative	8	1	13	0	26

*All the patients in these groups were negative seven through thirteen days after treatment. Their Coefficient of Infection was, therefore, equal to zero.

On the basis of these considerations, it is suggested that the intensity of infection be always considered in evaluating and comparing the anthelminthic activities of various drugs against *E. vermicularis*.

The rate of cure in the various groups seemed to be related to the frequency of positive tests during the initial period of observation or, in other words, to the intensity of infection as measured by the C.I. As

tend the observations reported by Jung and Beaver.[5]

The quantitative determination of the relative intensity of infection could be extended to the examinations of the individual patient in medical practice. By giving a value of 1 to a patient found to be positive only once out of six daily consecutive examinations, 2 to a patient who was positive twice, and so forth up to 6 to a patient who was positive with every

examination, an indirect estimation of the relative worm burden can be made. This estimation can be of value in determining the intensity of infection for clinical and therapeutic purposes. Furthermore, it may throw some light on the degree of egg dissemination in the patient's immediate environment, thus having a bearing on the likelihood of infection among the persons he frequently associates with, primarily the members of his family.

In order to test whether the high proportions of negatives obtained with high dose levels with piperazine hexahydrate (Group II) and with phthalylsulfathiazole (Group IV) represent actual cures or just a temporary sterilization of the worms, the patients were re-examined for six consecutive days beginning with the sixty-seventh day after treatment was discontinued. The results are summarized in Table IV. Since six individuals of Group II left the ward or were transferred during that period, they were not included in the follow-up studies. Also, one patent of Group IV, who remained positive after treatment, is not included in the table. It is of interest to notice, however, that this patient was negative when re-examined for six consecutive days sixty-seven days after treatment. Group II A and Group IV A indicate the persons in wards II and IV who had become negative after treatment. A perusal of Table IV shows that more than two months after treatment only a few individuals in each group had become positive. That these cases represent reinfections and not relapses is evidenced by the fact that no significant difference existed in the Group II A and Group IV A and their respective controls II B and IV B. The C.I. also remained low with no significant or consistent differences in the various groups.

SUMMARY

Of 265 patients in a mental institution examined for the presence of *Enterobius vermicularis* infection, 200, or 75 per cent, were found to be positive. The prevalence and intensity of infection were determined by six consecutive daily examinations of cellulose tape slide preparations.

A marked reduction in the prevalence and intensity of infection was observed following treatment with relatively high dosages of piperazine hexahydrate or phthalylsulfathiazole for fourteen consecutive days. The effect of treatment with these drugs was still evident more than two months after therapy.

RO 2-5655/3, in the amounts used, was of very limited value in reducing the prevalence of infection. It produced, however, a moderate decrease in the intensity of infection.

Although spontaneous apparent cures were observed in the untreated controls, no marked changes in the intensity of infection occurred during the period of observation. The rate of spontaneous cure in the untreated controls and the degree of effectiveness of the drugs tested were somewhat related to the intensity of infection. These results suggest the use of a coefficient of infection in comparing the therapeutic effectiveness of various drugs.

We are greatly indebted to Dr. Harry Most, Professor of Preventive Medicine, New York University, for his suggestions on the drugs to be used in this investigation. We also wish to express our appreciation to: Burroughs Wellcome & Co., Tuckahoe, New York; Sharp & Dohme, Philadelphia, Pennsyl-

vania; and Hoffmann-LaRoche, Inc., Nutley, New Jersey, for providing the Florida Farm Colony, Gainesville, Florida, with generous supplies of piperazine hexahydrate (Antepar), phthalylsulfathiazole (Cremothalidine), and RO 2-5655/3, respectively.

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A Letter From Virginia

I now send you the most satisfactory Account I am able, of the dissimilar Birth you have heard me mention with Wonder.

A young Negroe Wench of Col. Mason's began to breed early, and had at the first Birth a Negroe Child. Soon after she was delivered of two, a Mulatto Girl, and a Negroe Boy, named Austin; though born at one Time, they were believed in the Family to be Children of different Fathers, as besides her Negroe Husband, it was well known that the Overseer, a white Man, called Thomas Plum, kept Company with her, to the no small Uneasiness of her black Husband. But the Appearance of the Children was a Proof stronger than any Witnesses; for Austin was as black a Negroe as I ever saw, and had short, curled, woolly Hair; and in every other Respect was like other Negroes. The Twin Sarah, was as remarkably white, with blue Eyes, and long black Hair, that reached to her Waist. The Wench at the next Birth was delivered of three Children, of which two were Mulattoes, and the other a Negroe.

From VIRGINIA GAZETTE (Hunter), Dec. 1, 1752.

THE TREATMENT OF WILMS' TUMOR

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IN 1947, Silver[1] summarized the experience at the University of California Hospital in handling patients with Wilms' tumor (embryoma of the kidney). His report was based on a series of eighteen patients, covering the period from 1926 to 1944. The purpose of this report is to continue the series, bringing it up to date, as of 1954, and adding an additional nine patients. This represents ten years' additional experience, during which time there were 13,656 hospital admissions on the Pediatrics Service. As before, the series includes all patients admitted to the University of California Hospital with a diagnosis of Wilms' tumor confirmed by microscopical examination of surgical or autopsy material.

Although an infrequent lesion, Wilms' tumor remains the most common abdominal malignancy of infancy. Interest originally centered on its unusual and varied microscopic appearance, with speculations as to its origin. It is now generally accepted that these highly malignant tumors arise from primitive mesodermal cells displaced from the renal blastema during development. Many excellent articles[2, 3] have been written regarding the pathology, natural history, and clinical features of this tumor. More recently, with the realization that high survival rates are possible with prompt treatment, interest has centered on determining the best possible treatment.

The clinical findings in the present series of patients are listed in Table I. Pertinent comments follow.

AGE

Wilms' tumor is primarily a disease of infancy, with the majority of the patients less than 3 years of age. In the nine patients seen since 1944, six were 3 years or younger. One each was 4, 6, and 18 years of age. Excluding the 18-year-old patient (C. B.), the average patient was slightly less than 3 years of age (2.8 years). For the entire group of twenty-seven seen since 1926, the average age was 4.8 years.

SEX

No sexual predominence has been found. In the present group of nine, there were five boys and four girls. In the total group, there were twelve boys and fifteen girls.

SYMPTOMS

As in the previous series, symptoms as a rule did not appear until the tumors had become quite large and easily palpable. The most frequent complaint was that of a mass with or without associated discomfort in the abdomen; this was the presenting symptom in six of the nine patients. Fever was present in three patients.

From the Department of Radiology, University of California School of Medicine.
†Deceased September, 1955.

TABLE I. PATIENTS WITH WILMS' TUMOR OF THE KIDNEY

PATIENT	AGE	SEX	DATE OF ENTRY	FIRST SYMPTOMS	DURATION OF SYMPTOMS	BLOOD PRESSURE	TREATMENT				COURSE	COMMENTS
							PREOPERATIVE IRRADIATION	NEPHRECTOMY		POSTOPERATIVE IRRADIATION		
								DATE	APPROACH			
C. B.	18 yr.	F	3/45	Swelling of abdomen	2 mo.	115/80	–	–	–	–	Died 7/45	Biopsy only; multiple peritoneal implants
G. K.	7 mo.	F	11/46	Abdominal mass Microscopic hematuria	3 wk. On admission	–	–	11/46	Lumbar	3,000 r tumor in 25 da.	Died 7/47	Patient developed Wilms' tumor in opposite kidney 3/47; irradiation 4/47
J. F.	3 yr.	M	9/48	Abdominal mass	3 mo.	132/90	–	–	–	–	Died 9/48	Admitted with pulmonary and hepatic metastases; confirmed at autopsy
V. A.	16 mo.	M	2/49	Fever Abdominal mass	4 mo. 4 da.	128/62	2,500 r tumor in 19 da.	2/49	Transperitoneal	1,900 r tumor in 21 da.	Alive and well 8/55	Slight asymptomatic scoliosis of thoracolumbar spine
R. R.	19 mo.	M	4/49	Failure to gain weight Abdominal mass	4 mo. 2 wk.	90/70	2,500 r tumor in 21 da.	6/49	Transperitoneal	2,500 r tumor in 24 da.	Alive and well 10/54	Characteristic tumor calcification on roentgen examination
D. D.	3 yr.	F	9/50	Abdominal mass	1 wk.	110/80	–	–	–	–	Died 2/51	Bilateral Wilms' confirmed by laparotomy and biopsy; treated with nitrogen mustard with temporary benefit
G. T.	4 yr.	M	10/51	Abdominal mass with vomiting	3 mo.	120/70	2,500 r tumor in 29 da.	12/51	Transperitoneal	2,500 r tumor in 27 da.	Died 12/52	On 10/51, initial biopsy before institution of treatment; pulmonary metastases treated by x-ray in 1952 without benefit
Y. O.	6 yr.	F	9/52	Fever with purpura Abdominal mass	1 mo. 2 wk.	145 (systolic)	–	9/52	Transperitoneal	Yes*	Alive and well 8/55	
G. Y.	18 mo.	M	4/53	Abdominal mass	2 wk.	–	2,500 r tumor in 24 da.	5/53	Transperitoneal	2,500 r tumor in 24 da.	Alive and well 9/55	—

*Postoperative irradiation given by private radiologist.

Failure to gain weight was the presenting symptom in one patient. One patient showed microscopic hematuria and no gross hematuria was noted in any case. The blood pressure was elevated in two of the seven patients in whom it was recorded.

LABORATORY STUDIES

The usual laboratory tests were of little help in diagnosis. They were of value in the evaluation and management of the anemia, dehydration, and uremia that were present.

ROENTGENOGRAPHIC STUDIES

Thorough roentgenographic studies proved indispensable. Films of the chest and skeleton may demonstrate the presence or absence of metastases. Plain films of the abdomen may show calcification within the tumor. Steinbach and Brown,[4] in a study of retroperitoneal tumors in children, thought that the character of the calcification often is of aid in differential diagnosis between Wilms' tumor and neuroblastoma. The calcification in Wilms' tumor consists of dense, homogeneous streaks and concentric rings located in the periphery of the tumor. In neuroblastoma, the calcification usually has a fine, stippled appearance and is not limited to the periphery of the mass. These findings have been confirmed by Fulton and Evans.[5] Dickey and Chandler[6] felt that the presence of calcification was a good prognostic sign.

In the present group of nine patients, calcification was present in one patient and he has survived five years. Excretory urography was performed in every case to obtain information not only as to the relationship of the mass to the involved kidney but, also of equal importance, as to the status of the opposite kidney. In the present group of nine patients, one (D. D.) had bilateral involvement when first seen. Another (G. K.) showed a normal contralateral kidney preoperatively, but developed involvement of this kidney four months postoperatively.

TREATMENT

Since 1936, all patients without evidence of distant metastases have been treated with nephrectomy combined with radiation therapy. Nephrectomy for Wilms' tumor was carried out almost exclusively via the transperitoneal approach as advocated by Ladd and White.[7] This approach permits the early ligation of the renal pedicle and facilitates the mobilization and removal of even massive tumors.

On the basis of the previous experience, as reported by Silver,[1] in which all four of the patients receiving preoperative x-ray treatment survived, that method has been recommended in every instance in an effort to determine its worth. The usual plan has been to deliver a midplane tissue dose of 2,500 r in a period of from three to four weeks, using 200 KV x-rays with a HVL of 0.9 mm. of copper and a 50 cm. TSD. Anterior, posterior and, occasionally, lateral fields were used, depending on the size of the tumor. Due to the massive size of these tumors, the anterior and posterior fields usually crossed the midline. Care was taken to avoid irradiation of the opposite kidney. Nephrectomy was not carried out until three or four weeks after treatment in order to allow for the maximum effect of the radiation on the tumor to take place and to allow for the subsidence of the

reaction in the surrounding normal tissues. A second similar course of radiation therapy was carried out one to two weeks after nephrectomy. Two patients (G. K., Y. O.) did not receive preoperative irradiation because their pediatricians requested it to be omitted. Their tumors were smaller than average, facilitating initial surgical attack. The involved kidneys weighed 370 and 366 grams, respectively. These patients received a course of postoperative irradiation similar to the above, with the exception that the final tissue dose to the midplane was raised to 3,000 r.

Intensive supportive care was an essential feature of the preoperative radiation therapy. Hospitalization was generally recommended for at least the earlier phases of therapy. Anorexia was common; vomiting occurred occasionally. Leukopenia was not a problem, and anemia was controlled by blood transfusions as needed. The response to treatment was dramatic, the tumor shrinking to less than one-half of its original size. This was accompanied by a marked improvement in the general condition of the patient. At times the child appeared to be so well that the parents had to be reconvinced as to the necessity of nephrectomy. The postoperative course of radiation therapy caused almost no difficulty and was usually given on an outpatient basis.

Skin changes have generally consisted of a pigmented epidermitis which resolved by dry desquamation. Late changes were minimal, consisting principally of a barely perceptible dryness of the skin.

Skeletal changes have not been severe, consisting of decreased growth of the irradiated epiphyses. They correspond in a large part to the changes described by Neuhauser and associates.[8] In our present series, one patient (V. A.) has developed a slight scoliosis which has been asymptomatic. One patient (L. C.) from our previous group, whose tumor was discovered at 3 days of age, developed a kyphoscoliosis of the thoracolumbar spine which required a spinal fusion at age 6. The deformity has been arrested and the patient is now asymptomatic at age 12.

RESULTS

Of the nine patients in the present series, three had advanced disease when first seen. One (D. D.) received a trial of chemotherapy. The other two were treated symptomatically. All three are now dead. Of the remaining six, two were treated by nephrectomy and postoperative irradiation. One (G. K.) died following appearance of tumor in the opposite kidney. The other (Y. O.) is alive without evidence of disease three years following nephrectomy. The remaining four patients received preoperative irradiation, nephrectomy, and postoperative irradiation. Of these four, one (G. T.) died of pulmonary metastases fourteen months following treatment. The other three are alive five and one-half, six, and two and one-half years following treatment. Accepting one and one-half years as a suitable period of observation, as suggested by Gross and Neuhauser,[9] four of our present group of nine patients have survived (44 per cent). Of those who underwent nephrectomy, four out of six are alive and well (66.7 per cent).

The survivors from the previous series have now been followed for over

ten years. All are alive without evidence of disease with the exception of D. W., who died in 1953 of pulmonary tuberculosis and diabetes. She had survived over eleven years. Autopsy showed no evidence of malignancy. Of special interest is J. B., who had a postoperative pulmonary metastasis treated by radiation therapy in 1945. He is alive and well as of 1955 with no evidence of disease.

The combined series from 1926 to 1954 includes twenty-seven patients with fourteen survivors—an absolute survival rate of 52 per cent. Nineteen of the entire group of twenty-seven had nephrectomy. All of the survivors are from this group. Four patients treated prior to 1936 had nephrectomy alone. Of these, three have survived ten or more years. Seven patients have been treated by nephrectomy and postoperative irradiation. Of these, four have survived. Eight patients have been treated by preoperative irradiation, nephrectomy, and postoperative irradiation. Of these, seven have survived.

TABLE II. RESULTS OF TREATMENT FOR WILMS' TUMOR

TREATMENT	TOTAL	ALIVE	DEAD	PER CENT
Nephrectomy alone	4	3	1	75
Nephrectomy plus postoperative irradiation	7	4	3	57
Preoperative irradiation plus nephrectomy plus postoperative irradiation	8	7	1	87.5
Supportive (advanced disease when first seen)	8	0	8	0
Total	27	14	13	52

DISCUSSION

The problem of the best treatment for Wilms' tumor remains unsettled. A variety of methods have been used in the past.

Radiation therapy alone was used by Dean,[10] who obtained five survivors in his series of twenty patients with a clinical diagnosis of Wilms' tumor. Cures of single patients have been reported by Nesbit and Adams,[11] Bixler and associates,[12] Dickey and Chandler,[6] Benzing,[13] and others. They attest to the possibility of cure by radiation alone. Harvey,[14] in a review of 444 reported cases of Wilms' tumor treated by all methods, found ten cured by radiation therapy alone out of a total of sixty-three cases. The possibility of cure by radiation therapy alone, then, while well established, is low, and this method has been abandoned as the treatment of choice for Wilms' tumor.

Nephrectomy alone was, for a considerable period, the main form of treatment. As the last major advocate, Ladd and White[7] published in 1941 a series of sixty cases with fourteen survivors. Harvey[14] lists twenty-eight patients as surviving from a total of 180 reported as treated by nephrectomy alone.

The value of combining some form of radiation therapy with nephrectomy was readily appreciated and was used early as a preoperative measure when the tumor was felt to be too large for initial surgical attack. This formed a particularly unfavorable group. Nonetheless, Harvey was able to collect five survivors out of a total of twenty-seven reported as receiving

treatment consisting of preoperative x-ray treatment followed by nephrectomy.

The next logical extension of radiation therapy was the use of postoperative irradiation in those patients in whom the surgical removal of the tumor was known to have been incomplete. Nesbit and Adams[11] reported two such cases with survival. More recently, Gross and Neuhauser[8] have reported significantly improved survival rates since the institution of routine postoperative irradiation, with eighteen survivors from a group of thirty-eight patients (47.4 per cent). Harvey[14] collected thirty-three reported survivors from a total group of 109 patients so treated.

The use of preoperative irradiation together with nephrectomy and postoperative irradiation has been advocated by Priestley and Schulte,[15] Rusche,[16] and Garrett and Mertz.[17] Harvey[14] collected twenty-one reported survivals following this form of treatment in a total of sixty-five patients reported as so treated. Since then Garrett and Mertz[17] have reported five survivors out of six patients so treated.

The technical advantage of this method in facilitating the subsequent removal of the tumor by decreasing its size and vascularity has been stressed by Priestley and Schulte.[15] Any increase in survival remains to be established. In our series, seven of eight patients treated by this method have survived. In no instance have metastases appeared during the course of treatment. Our series remains too small for any definite conclusions. However, it suggests that preoperative irradiation in conjunction with nephrectomy and postoperative irradiation does not jeopardize the patient's chances of survival and may actually increase them.

CONCLUSION

1. The University of California Hospital series of Wilms' tumors now consists of twenty-seven cases covering the period of 1926 to 1954.

2. Fourteen patients have survived for two and one-half years or more; an absolute survival rate of 51.8 per cent.

3. Of those who underwent nephrectomy with or without irradiation, fourteen out of nineteen have survived (73.6 per cent).

4. Of those who underwent nephrectomy without irradiation (none since 1936), three out of four survived (75 per cent).

5. Of those who underwent nephrectomy and postoperative irradiation, four out of seven survived (57 per cent).

6. Of those who underwent preoperative irradiation, nephrectomy, and postoperative irradiation, seven out of eight have survived (87.5 per cent).

7. A relatively favorable prognosis for patients having Wilms' tumor, when adequately treated, is reaffirmed.

8. Further trial of preoperative irradiation, nephrectomy, and postoperative irradiation in unselected cases appears warranted.

Sincere thanks for permission to report these cases are expressed to the Departments of Pediatrics, Urology, and Surgery of the University of California School of Medicine.

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In this Scab *little blisters* are wont first to break out, *in any part of the Skin*, but especially *the face, ears, or arms*, sometimes *almost over the whole body;* with *a great itching;* by reason of which Infants, if they can, do scratch the parts affected, and if they cannot, they rub their face at any thing they meet with, nor do they leave off, although after rubbing the parts be red, and *the outer skin opened*, and both *a sharp and biting Liquor*, and also *Blood* runs out: by all which *the evil* is not lessened but rather *encreased*, by *spreading more*, and *breeding new trouble elsewhere.*

From FRANCIS SYLVIUS, 1674.

THE INFLUENCE OF BREAST FEEDING ON WEIGHT GAIN IN INFANTS IN THE FIRST YEAR

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SINGAPORE

PEDIATRICIANS are agreed that breast milk is the most suitable food for young infants and that breast feeding is highly desirable for the well-being of the child. There are a number of studies relating the incidence of morbidity and mortality to the method of feeding, but the influence of breast feeding on weight gain has received little attention, although it is a generally accepted principle that in infancy a regular and satisfactory gain in weight is an indication of good health and nutrition. This investigation was undertaken to study the weight gain in three separate groups of infants of different ethnic origin and economic circumstances.

SELECTION OF STUDY GROUPS

During the first year, the weight of a child at any particular age is influenced by inherited characteristics and by postnatal environment[1, 2]; therefore the infants were selected so that the economic level, the housing, and standard of hygiene of the families were uniform throughout each study group.

Three studies were made in Singapore between the years 1951 and 1954. The selection of infants was based on the following criteria:

(1) Both parents were of pure ancestry but the length of sojourn in Singapore was not taken into account.

(2) The infants were born to women confined in the Kandang Kerbau Maternity Hospital.

(3) Only single births were considered and the infants were classified as physically mature by the medical staff of the hospital but infants were excluded if they had congenital defects.

(4) The infants were domiciled in the urban area so that regular home visits could be made to obtain complete and accurate records.

(5) The families within each study were of similar economic level of society and were selected on the basis of hospital admission as follows: in study A, Southern Indian infants, mainly Tamils from poor families, in study B, Chinese infants from poor families, and in study C, Chinese infants from families in the middle and upper income groups.

In Singapore, there is little seasonal change and no significant difference was found between the average birth weights of infants in different months; therefore, the time of the year was not taken into account when the selection was made.

Details of the experimental procedure in studies A and B have been published.[3-6] In study C, all infants (sixty-nine males and sixty females), who fulfilled the requirements between Feb. 2, 1953, and Nov. 29,

From the Department of Social Medicine and Public Health, University of Malaya.

1953, were included. During the year, the study of three infants was discontinued as the families refused to cooperate. Two infants died, one at 39 weeks and one at 42 weeks, with gastroenteritis, and ten families moved into areas which were not accessible to the investigators.

Comparisons were made between the study groups and the hospital population in the same year with reference to the range of maternal ages and birth ranks, birth weights, and lengths of the infants. The differences were not significant and in these factors the study groups were not unrepresentative of the hospital population.

TABLE I. DISTRIBUTION OF INFANTS ON BASIS OF DURATION OF BREAST FEEDING

CLASSIFICATION	NUMBER OF INFANTS					
	INDIAN STUDY A*		CHINESE STUDY B		CHINESE STUDY C	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
Group 1 Breast feeding < 12 weeks	16	22	16	14	29	30
Group 2 Breast feeding 12 < 24 weeks	15	10	5	4	11	14
Group 3 Breast feeding 24 < 48 weeks	10	12	16	19	15	7
Group 4 Breast feeding 48 or more weeks	9	12	20	9	5	3
All groups	50	56	57	46	60	54

*Millis.[4]

COLLECTION OF DATA

The birth weights were recorded at the hospital, where the infants were weighed to the nearest ounce by the hospital staff in the labor ward within a short time after birth. All subsequent weights were obtained by the staff of the Division of Applied Nutrition in the baby's home and the same infant beam-balance, "The Cromwell House Baby Scale," was used throughout the experimental periods. Each baby was weighed naked to the nearest half ounce at approximately the same time each day, namely, between 9:30 and 11:30 A.M. The babies were weighed at two-week intervals for twelve weeks and thereafter at four-week intervals until the end of the first year.

There were 1,980 visits to the homes of infants in study A, 2,055 in study B, and 2,172 in study C. At each visit, information was collected about the environment and health of the infants. The method of feeding the baby was recorded, together with the date of initiation of any change in the routine.

RESULTS AND DISCUSSION

This report is limited to the infants with complete records from birth to the end of the first year, namely, fifty males and fifty-six females in study A, fifty-seven males and forty-six females in study B, and sixty males and fifty-four females in study C.

TABLE II. THE MEAN WEIGHTS (OUNCE) OF INFANTS AT DIFFERENT AGES IN RELATION TO METHOD OF FEEDING

AGE (WEEKS)	POOR INDIAN (STUDY A)		POOR CHINESE (STUDY B)		WEALTHIER CHINESE (STUDY C)	
	GROUP 1* BREAST FED <12 WEEKS (38)‡	GROUPS 3 AND 4 BREAST FED 24+ WEEKS (43)	GROUP 1† BREAST FED <12 WEEKS (30)	GROUPS 3 AND 4 BREAST FED 24+ WEEKS (64)	GROUP 1 BREAST FED <12 WEEKS (59)	GROUPS 3 AND 4 BREAST FED 24+ WEEKS (30)
0	98	103	111	110	110	117
4	113	125	131	141	133	150
8	138	155	160	175	161	185
12	155	179	183	201	186	214
16	173	199	204	222	208	233
20	190	215	220	237	227	249
24	203	229	232	248	242	260
28	215	241	244	257	256	270
32	226	250	252	264	269	277
36	234	258	263	270	279	287
40	243	264	272	276	288	295
44	251	271	279	282	297	303
48	256	277	289	289	304	308
52	264	283	295	294	313	313

*Millis.[4]
†Millis.[6]
‡Number of infants.

TABLE III. ANALYSIS OF VARIANCE OF BIRTH WEIGHT BETWEEN BREAST-FED AND ARTIFICIALLY FED INFANTS

DESCRIPTION	SOURCES OF VARIANCE	SUMS OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	REMARKS
Males						
Poor Indian						
	Within groups	6930.2764	33	210.0084	2.5053	Not significant
	Between groups	526.1236	1	526.1236		
Poor Chinese						
	Within groups	9005.159	50	180.1032	1.0847	Not significant
	Between groups	195.361	1	195.361		
Wealthier Chinese						
	Within groups	10845.9079	46	235.7806	0.0000	Not significant
	Between groups	0.0721	1	0.0721		
Females						
Poor Indian						
	Within groups	7905.8221	44	179.6778	1.1436	Not significant
	Between groups	205.4829	1	205.4829		
Poor Chinese						
	Within groups	5833.2143	40	145.8303	1.8368	Not significant
	Between groups	267.8577	1	267.8577		
Wealthier Chinese						
	Within groups	8208.1667	38	216.0044	5.7184	Significant ($p < .05$)
	Between groups	1235.2083	1	1235.2083		

The infants were grouped on the basis of duration of breast feeding as follows:

Group 1, infants who were not breast fed or were weaned before they were 12 weeks of age.

Group 2, infants who were weaned between 12 and 24 weeks.

Group 3, infants who were weaned between 24 and 48 weeks.

Group 4, infants who were partly or wholly breast fed for 48 weeks or more.

Each group was not homogeneous as some infants were entirely breast fed whereas others received breast milk together with a variety of other foods, and, in addition, infants were weaned at different times within the stated periods. Table I shows the distribution of infants in these groups.

Considering each study separately, comparisons were made between the infants who were artificially fed before the twelfth week (Group 1) and those who were breast fed for 24 or more weeks (Groups 3 and 4). The mean weights of the infants in the various feeding groups in relation to age are presented in Table II and it would appear that breast feeding had influenced the weight.

However, the weight of an infant during the first year is dependent on birth weight,[2, 7] and in infants of

TABLE IV. ANALYSIS OF VARIANCE OF WEIGHT GAIN AT 24 WEEKS BETWEEN BREAST-FED AND ARTIFICIALLY FED INFANTS

DESCRIPTION	SOURCES OF VARIANCE	SUMS OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	REMARKS
Males						
Poor Indian						
	Within groups	16525.6218	33	500.7761		
	Between groups	4377.8782	1	4377.8782	8.7422	Significant ($p < .01$)
Poor Chinese						
	Within groups	21614.9764	50	432.2995		
	Between groups	4905.9456	1	4905.9456	11.3485	Significant ($p < .01$)
Wealthier Chinese						
	Within groups	31388.3634	46	682.3557		
	Between groups	71.1571	1	71.1571	0.1043	Not significant
Females						
Poor Indian						
	Within groups	23065.9546	44	524.2262		
	Between groups	4001.1604	1	4001.1604	7.6325	Significant ($p < .01$)
Poor Chinese						
	Within groups	14763.4426	40	369.0861		
	Between groups	1674.1066	1	1674.1006	4.5358	Significant ($p < .05$)
Wealthier Chinese						
	Within groups	26893.242	38	707.7169		
	Between groups	1390.602	1	1390.602	1.9649	Not significant

similar economic circumstances, birth weight and subsequent weight have been shown to be influenced by sex.[2]

It is essential that birth weight and sex are taken into account when weights of infants are compared. Parfit,[8] Lowe and Gibson,[9] Millis and Tye[2] have also shown that weight gain was not related to birth weight; therefore, in this paper an analysis of variance was undertaken to determine the significance of the difference in weight gain between feeding groups at 24 and 52 weeks.

The summaries of these analyses are presented in Tables III, IV, and V. At 24 weeks, the breast-fed infants of poor families had a significantly greater gain in weight than the artificially fed infants but this advantage had been lost at 52 weeks. This finding is in agreement with Dean[10] who reported no relationship between the weights of infants at one year and the method of feeding. However, breast feeding made no difference to the weight gain at 24 weeks of infants of the higher income families, and at one year the artificially fed males were significantly heavier than the males who had received breast milk. Simpson[11]

TABLE V. ANALYSIS OF VARIANCE OF WEIGHT GAIN AT ONE YEAR BETWEEN BREAST-FED AND ARTIFICIALLY FED INFANTS

DESCRIPTION	SOURCES OF VARIANCE	SUMS OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	REMARKS
Males						
Poor Indian						
	Within groups	22460.6299	33	680.6251	1.9728	Not significant
	Between groups	1342.7166	1	1342.7166		
Poor Chinese						
	Within groups	23400.494	50	468.0933	0.4559	Not significant
	Between groups	213.367	1	213.367		
Wealthier Chinese						
	Within groups	52956.0514	47	1126.7245	4.5103	Significant ($p < 0.5$)
	Between groups	5081.8561	1	5081.8561		
Females						
Poor Indian						
	Within groups	36637.990	44	832.6816	2.1894	Not significant
	Between groups	1823.065	1	1823.065		
Poor Chinese						
	Within groups	16722.6166	40	418.0654	2.8525	Not significant
	Between groups	1192.5264	1	1192.5264		
Wealthier Chinese						
	Within groups	44617.7417	38	1174.1511	0.0043	Not significant
	Between groups	5.0023	1	5.0023		

and Stewart and Westropp[12] published similar findings for infants in England.

Within each study, the economic level, the standard of housing and hygiene of the families varied very little, and the difference in birth weight between feeding groups was not significant; therefore, the differences in weight gain could be attributed to the method of feeding. Detailed descriptions of the weaning diets of studies A and B have been published[4, 6] and it was apparent that these diets did not supply adequate amounts of essential nutrients. In general, the infants in study C received a weaning diet which are more likely to meet the requirements of growth.[13] The standard of housing was satisfactory and the level of hygiene considerably above that of the poor infants. The difference in response between poor and wealthier infants can be directly attributed to a more adequate weaning diet and a higher standard of hygiene in families in better financial circumstances.

In conclusion, this investigation has shown that breast feeding results in a greater weight gain at 24 weeks for poor Indian and Chinese babies but no significant difference was found for wealthier Chinese babies. The weaning diet of the wealthier babies was more adequate and the standard of hygiene was higher and therefore the artificially fed babies were at no disadvantage. The poor babies received an inadequate diet after weaning and consequently at 12 months the benefits resulting from breast feeding were no longer obvious.

I wish to thank Mr. Tye Cho Yook for his advice in the statistical aspects of the paper.

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TRANSIENT SYNOVITIS OF THE HIP

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THE commonest cause of painful hip in children in the United States today is a condition known as transient synovitis of the hip. It is a self-limited disease rarely lasting more than a few weeks and often only a few days. It may cause severe pain and be extremely disabling, with such general symptoms as fever and an elevation in the white blood count, or it may be so fleeting and mild as to cause nothing more than a slightly discernible limp without other positive physical findings. It is a condition seen uncommonly by the resident pediatricians because it is rarely of sufficient severity to warrant hospitalization.

ETIOLOGY

A review of thirty-six cases with follow-up of from six months to eight years has failed to reveal any consistent etiological factor in our series. Trauma, upper respiratory infection, allergy, localized thromboembolic phenomena, and hysteria have all been suggested as possible etiological factors. Finder[5] pointed out that hip pain with limp and muscle spasm with or without mild generalized symptoms was common to any disease of the hip in its earliest stage and that the condition which we know as transient synovitis of the hip may in reality be an abortive septic condition in which the immunity and natural resources of the patient have been able to overcome a local invader. Actually the benign self-limited nature of this syndrome has mitigated against the establishment of an etiological factor. None of our cases and few in the literature have been biopsied. No specific etiology has been determined. Even simple aspiration with smear and culture has rarely been done. In our series the youngest patient was 2½ years and the oldest was 12 years. All but five of the patients were in the 3- to 7-year age group. Twenty-nine of our patients were boys and seven were girls. The left hip was involved twenty-five times and the right hip eleven times. No patients had bilateral disease and no patients had recurrences, although one boy, aged 5, seen at intervals over a period of three years, occasionally complained of slight pain and limp, but no positive physical, laboratory, or roentgenographic findings could ever be found.

SYMPTOMS

The symptoms vary from such mildness that children for whom appointments were made two or three days earlier show no signs or symptoms on the day of their examination. Patients with more severe cases may be carried to the office in great pain, are frightened and apprehensive, have not slept or eaten, and usually hold the involved hip in a position of flexion, adduction, and internal rotation (Fig.

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1). The onset of symptoms may vary from a vague ache, with or without a slight limp which may have been present intermittently for a number of days or weeks, to a sudden acute onset of severe pain with inability to walk, night crying, vomiting, and fever. The degree of limp has often seemed to vary during the examination and some children who were carried into the office were able to depart with only a slight limp. The history too has suggested that the severity of symptoms has varied during the course of the disease. A limp is present in a great majority of the cases and those who did not limp at the time of examination usually had a history of having had a limp. Pain was present in a majority of the patients and those who did not have pain on examination had had some degree of pain previously. Most of the patients exhibited tenderness over the hip joint anteriorly and in a number of these there was palpable swelling in this region. Limitation of extension, abduction, and external rotation were by far the commonest signs of joint involvement. A positive Trendelenburg sign was elicited in a number of the patients, probably as a re-

TABLE I

INITIALS	SEX	AGE (YR.)	TEMPERATURE	W.B.C.	SED. RATE	DAYS' DURATION
L. G.	F	7	99°	Normal	–	13
B. A.	M	5	Normal	–	–	10
M. S.	F	12	101°	Normal	Normal	12
M. B.	M	4	Normal	–	–	14
J. S.	M	2½	Normal	Normal	Normal	17
I. R.	F	7	Normal	–	–	13
L. W.	M	5	Normal	–	–	8
L. E.	M	8	99.4°	9,800	Normal	27
N. A.	M	7	Normal	–	–	19
R. G.	M	7	Normal	–	–	13
D. K.	M	5	Normal	–	–	13
M. Z.	M	5	100.2°	–	–	16
I. V.	M	6	Normal	–	–	14
I. G.	F	5	Normal	–	–	17
R. S.	M	5	Normal	–	–	19
C. M.	F	6	99.8°	Normal	Normal	10
J. O.	M	3	Normal	–	–	6
M. C.	M	4	Normal	–	–	13
M. J.	M	4	Normal	–	–	17
T. S.	F	6	Normal	–	–	12
E. K.	M	5	Normal	–	–	7
J. H.	M	4	Normal	–	–	11
M. L.	M	7	99.2°	9,800	–	16
K. S. L.	F	6	Normal	–	–	7
R. H.	M	3	Normal	–	–	21
R. C.	M	5	Normal	–	–	20
S. L.	M	6	Normal	–	–	10
P. R.	M	8	99.8°	10,400	14	18
T. S.	M	7	99.4°	–	–	14
J. S.	M	11	Normal	–	–	9
P. H.	M	6	Normal	–	–	14
R. T.	M	3	Normal	–	–	7
E. W.	M	6	Normal	–	–	8
B. R.	M	7	Normal	–	–	10
R. K.	M	5	Normal	–	–	9
J. J.		3	Normal	–	–	14

sult of an attempt to avoid painful abduction (Fig. 2). The same patient sometimes showed limitation of both external (Fig. 3) and internal rotation (Fig. 4) of the hip. Full abduction of the involved hip was usually not possible (Fig. 5). The limitation of motion was sometimes slight and in a few mild cases there was no limitation of motion at all. Only a few patients showed a brief elevation of temperature and in no case was the temperature over 101° F. Four patients had temperatures over 100° F. Two of these had white blood counts and differential counts performed and both were within the limits of normal. All patients had roentgenograms of the pelvis to include both hips. No changes in the bone architecture were seen in any of the cases. There are reports[3] to the effect that enlargement of the obturator, iliopsoas, or gluteus medius muscle or of the capsular shadow is pathognomonic roentgenographic evidence of synovitis of the hip. We have reviewed our films and found that though there was often an inequality in these soft tissue shadows on either side, there was no consistent relationship between the side showing the larger shadows and the involved hip.

Fig. 1.—Position of flexion, adduction, and internal rotation commonly seen with transient synovitis and also with any other hip disease.

Fig. 2.—Positive Trendelenburg sign. When standing on the involved right hip the buttock is lower on the normal side due to inability of the involved side gluteal muscles to abduct the pelvis. In transient synovitis this is not a constant sign and when it does occur is probably the result of attempt to avoid painful abduction. This sign is also present in dislocation of the hip because the gluteal muscles have no solid hip fulcrum to work against and may be present when there is weakness of the gluteal group rendering them powerless to abduct the pelvis over the hip.

TREATMENT

In our series only one patient was hospitalized and this was a 12-year-

old girl who had a temperature of 101° F. and the diagnosis of transitory synovitis was not immediately suspected. After one week in bed with five pounds of traction the symptoms subsided, and the patient has remained asymptomatic for five years. This was the only patient in our series in whom traction was necessary. Finder reported that a few severe cases required immobilization in a plaster spica. These were undoubtedly more persistent than any of our cases and their duration of symptoms was many months. In our series the duration of symptoms has ranged from six to twenty-seven days and has averaged 13.3 days. Treatment has been bed rest, hot baths, and analgesics.

Fig. 3.—External rotation is usually best measured with the hips and knees both flexed, and is markedly limited on the involved right side.

Fig. 4.—Internal rotation is best measured with the patient in the prone position and with the knees flexed to 90 degrees.

DIAGNOSIS

Bradford and Lovett[1] stated that "the diagnosis of transitory synovitis should be made only when recovery has occurred." We feel that "the working diagnosis" should be evident on first examination. Transitory synovitis of the hip must be differentiated principally from septic arthritis either of tuberculous or pyogenic origin. Differentiation from tuberculous arthritis is almost invariably possible by roentgenogram. The tuberculous hip shows early generalized osteoporosis in the region of the involved joint and later there may be some narrowing of the joint space as well as bone destruction; if symptoms persist beyond a few weeks tuberculin testing is definitely indicated. Differentiation from pyogenic arthritis of the hip can be made on the basis of a high spiking fever and elevated white blood count. Roentgenograms are of no help in the early diagnosis of purulent arthritis but may rule out the presence of a bone tumor. Subperiosteal spiral fracture of the tibia is a common cause of pain and inability to walk in children of this age group and should not be overlooked. The age incidence of Perthes' disease coincides with the age incidence of patients with transitory synovitis of the hip, but in our series none of these patients has developed Perthes' disease. The diagnosis of poliomyelitis may be entertained and require a spinal fluid cell count to be ruled out.

Fig. 5.—The involved right hip cannot be fully abducted.

Butler[2] in 1933 coined the term "observation hip" because at that time in England about one-half of the children with hip symptoms who could not be diagnosed immediately, with

further observation, showed tuberculous hip disease. During the interval covered by this series we have not seen a single case of tuberculous arthritis and only one case of pyogenic arthritis of the hip.

CONCLUSION

A painful hip, once fraught with serious implications, still merits attention and observation, but with a much less fearful prognosis.

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The Dangers of Play

Though Children are not so much frightened by that dancing, yet there are some sports for them to be dallyed withall, for it falls out sometimes, that Children in that dancing are let fall, which can it be done without hurt unto the Child? I have seen a Father taking his little boy by the shoulder, and threw him upward, the sport pleased the boy very well, desired his father to do it again and again; this pastime pleased Father and Son for a while, but one time the boy being flung too high, and turning in that flinging came out of his Fathers reach, fell down behind his Father, who was not able to stay him then in his fall. This sport was turned into lamentation.

From FELIX WURTZ, 1565.

HYPOPITUITARISM, HYPOADRENALISM, AND HYPOGONADISM IN THE NEWBORN INFANT

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THE simultaneous occurrence of hypopituitarism, hypoadrenalism, and hypogonadism in the newborn infant has not been reported previously. The purpose of this paper is (1) to report a case, (2) to review recent observations in experimental fetal endocrinology, and (3) to review the pathologic findings of anencephalic monsters. The endocrine pathology of the patient reported will then be compared to that of anencephalic monsters and of animals hypophysectomized in utero and subsequently brought to term.

CASE REPORT

History.—J. H. was born to a gravida ii, para i, white female following an uneventful pregnancy. The child breathed and cried lustily immediately after birth. Shortly after birth, intermittent cyanosis was noted and oxygen was administered. The possibility of Rh incompatibility prompted transfer to this hospital.

Interrogation of the family revealed the first child to be normal, as were all siblings and relatives of the parents. There were no congenital anomalies on either the paternal or maternal side of the family, and none of the siblings of the parents had had miscarriages.

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On arrival at this hospital, at 9:30 A.M., the infant was dusky, but no pallor or hyperpigmentation was noted. Attention was immediately focused on the genitalia as the phallus was notably small for a male newborn infant, although the urethral opening normally penetrated the glans. The scrotum was small and flat, not distensible, and poorly striated. The gonads were not palpable in the scrotum, on the perineum, or in the inguinal canals. No other gross abnormalities were noted.

The red blood count on admission at 9:30 A.M. was 6.21 million per cubic millimeter; hemoglobin, 20.5 grams per cent; white blood count, 25,700, with a normal differential count; Rh type, positive; direct Coombs' test, negative. Laboratory findings on blood drawn at 12:30 P.M. were: sodium, 142 meq. per liter; chloride, 114 meq. per liter; hematocrit, over 80. An insufficient quantity of serum was obtained for other studies. An attempt to collect urine for 17-ketosteroid determinations was unsuccessful.

Oxygen was administered for intermittent cyanosis, which became progressively more s e v e r e. Apneic periods supervened, and in spite of stimulants and artificial respiration the infant died at 3:00 P.M.

At autopsy the infant's length was 21 inches and the weight, 8 pounds 4 ounces. The external appearance was unremarkable except for the genitalia described above. Examination of the head revealed a brain fully developed except that no hypophysis or infundib-

ulum was demonstrable. The diaphragma sellae lay tightly over a small sella which was approximately half normal size; the opening through which the infundibulum normally passes was not present. A small amount of fibrous tissue lay between the base of the brain and the diaphragm, but under the diaphragm the sella was empty. The adrenal glands were distinctly small, the combined weight being less than 1 gram. Testes were found lying along the pelvic wall in the normal route of descent and were notably smaller (combined weight 1 gram) than the testes of normal newborn infants. The thyroid weighed 1 gram and was grossly normal. The thymus weight was 16.5 grams (moderately enlarged) but was otherwise not unusual. No examination was made of the prostate. The pancreas was normal as were the other organs.

On microscopic observation, no pituitary tissue could be identified in either the fibrous tissue at the base of the brain or in the sella after decalcification. Fourteen hundred sections of the sella were made and each twenty-fifth section examined. Unfortunately, the area between the posterior pharynx and the sella was not examined.

The adrenal glands (Fig. 1, *C*) were devoid of fetal cortex except in a few scattered areas where minimal amounts persisted. The contracted zona glomerulosa consisted of poorly formed, rounded masses of cells that varied in size and occasionally extended into the narrow zona fasciculata, but the zones were poorly differentiated. The cells of the zona fasciculata had small, round, moderately stained nuclei with fine to course chromatin material. Fat stain demonstrated excessive lipid in this zone (Fig. 2, *C*). No medulla was observed in many of the sections and was abnormally thin in the remainder. Large, rounded hyperchromatic nuclei and a narrow rim of pale basophilic cytoplasm were characteristic of the few cells present.

Various-sized follicles lined by cuboidal type epithelium were present in the thyroid; colloid material was pale, and no vacuolization was present. The interstitial tissue was moderate in amount and was sparsely cellular connective tissue.

The thymus had a fully definitive cortex. Hassall's corpuscles were present but small. The over-all appearance was otherwise as expected. The lymph nodes revealed a moderate reactive hyperplasia.

The testes (Fig. 3, *C*) were remarkable in that there was complete absence of interstitial cells normally found in the newborn infant, and there was a marked excess of interstitial connective tissue. The tubules of the testes were lined by columnar undifferentiated epithelium. The epididymides were normal.

The other organs revealed no pathologic changes.

REVIEW OF LITERATURE ON EXPERIMENTS IN FETAL ENDOCRINOLOGY

The occurrence of hypoadrenalism and hypogonadism is frequently secondary to hypopituitarism. For this reason experiments in fetal endocrinology where hypopituitarism had been produced are deserving of review. In considering these experiments it is necessary to remember that in the fetus the peripheral endocrine glands are probably not entirely dependent upon the fetal pituitary but have two other sources of hormones: placental and maternal.

Raynaud and Frilley, as cited by Jost,[1] performed experimental hypophysectomy on fetal mice by irradiation of the pituitary. Wells[2] performed experimental hypophysectomy on the rat fetus by decapitation and brought the fetus to term in the maternal abdominal cavity. Jost and co-workers[1, 3-9] decapitated fetal rabbits and perfected a technique for carrying the fetus to term in utero.

The effect of these experiments on sexual differentiation varies in the different species. In rats and mice, hypophysectomy had essentially no effect.[1-3, 8, 9] In rabbits decapitated prior to the twentieth day of gestation, normal sexual differentiation of the genital ducts occurred, the müllerian ducts developing in the females and the wolffian ducts in the male, although the prostate was markedly reduced in size. The external genitalia, in contrast to the internal ducts, did not follow the normal pattern, as all rabbits decapitated on or before the nineteenth day developed female external genitalia regardless of chromosomal sex. Fetuses decapitated on the twenty-fourth day developed external genitalia compatible with their sex. Males decapitated between the nineteenth and twenty-fourth day developed external genitalia varying between the female and male pattern with incomplete fusion of the labial-scrotal folds and hypospadias.[1, 3-9] Jost and co-workers[1, 3-9] were able to correlate the degree of development with the quantitative discharge of granules from the McManus positive cells of the pituitary at the time of hypophysectomy, no granules being present on the nineteenth day, but a progressive number appearing from the nineteenth to the twenty-fourth day, when the granules disappeared, probably having been discharged. Jost[8, 9] also found a clearly demonstrable reduction, but not complete absence, of interstitial Leydig cells of rabbits' testes. The cytoplasm in these cells was reduced. The testes of decapitated rats also had a decreased number of interstitial cells.[2]

The adrenal glands in all species undergoing these experiments were invariably atrophied.[1-7, 10] Wells[10] has been able to prevent the atrophy of these glands in the rat by giving a single injection of corticotropin to the headless fetus at the time of decapitation.

Study of the thyroid gland histologically following hypophysectomy in the fetus has revealed various findings. In mice, as cited by Jost,[1] the thyroid was small and contained very little colloid. In the same article, Jost notes that Foote and Foote found that the follicles were normal in hamsters but that the total number of follicles was reduced, as was the volume of the gland. In rabbits it was demonstrated that there was no histologic difference between the decapitated fetus and control animals of the same weight, although functionally the thyroid gland was inadequate as proved with I^{131} uptake studies.

Growth was apparently not affected by hypophysectomy.[1, 3] From this the deduction can be made that endogenous somatotropin is not necessary for intrauterine growth, although it has been extracted from the hypophysis of the 9 cm. pig embryo.[11] The significance of this finding remains to be determined.

The effect of experimental hypophysectomy on the parathyroid glands, the pancreas, and the thymus has not been investigated to the best of our knowledge.

REVIEW OF ENDOCRINE PATHOLOGY IN ANENCEPHALIC MONSTERS

The human anencephalic monster closely approximates the experimental hypophysectomy performed on animal fetuses. It is as if this is nature's own experiment.

Hypopituitarism is a well-documented finding in anencephalic monsters.[12-16] It was initially believed that no pituitary tissue was present in many of these infants, while others manifested underdevelopment of the gland. It is now accepted that the anterior lobe is always present, but usually hypoplastic, and often can be demonstrated only by intensive search. Covell[13] found the pituitary gland present in each of thirty-two monsters examined; in seventeen examined in detail, six had all three lobes, eleven were without a pars nervosa, and only four of these had a pars intermedia. Twenty monsters examined by Angevine[12] had a pars anterior, although only five had a pars nervosa and six a pars intermedia.

There have been no reported abnormalities of sexual differentiation in anencephalic monsters. In Angevine's series[12] there were five males and fourteen females. In this series no abnormalities were noted in the gonads, as compared to the gonads of control infants of the same weight. Browne,[15] however, refers to a female anencephalic he examined who had hypofolliculism of the ovaries. In a second article[16] he refers to hypogonadism as being present in the typical pathology of the anencephalic monster but goes into no further detail.

Hypoplasia of the adrenal glands is constant in anencephalus.[12, 14] These glands typically weigh less than 1 gram, have no or markedly diminished fetal cortex, and have much lipid material in the zona fasciculata as contrasted to the normal.

The thymus is enlarged in this condition, and the individual lobules are described as being large with absence of the expected branching character.[14]

Thyroid histology as studied by Angevine[12] was normal in his series of twenty monsters.

Histologic structure of the pancreas and the parathyroid glands has not been reported.

DISCUSSION

The patient in this case report manifests many similarities to both experimentally hypophysectomized animals and an anencephalic monster used for comparison (Table I).

The hypoplasia of the adrenal glands is particularly striking. Comparison of this atrophy, histologically, with that of hypophysectomized animal fetuses is not possible because of basic structural differences in the animal and human adrenal.[1] Comparison of the adrenal glands of the patient reported and of the anencephalic monster which we studied (Figs. 1 and 2) reveals a marked similarity as noted by Potter[17] and Angevine.[18]

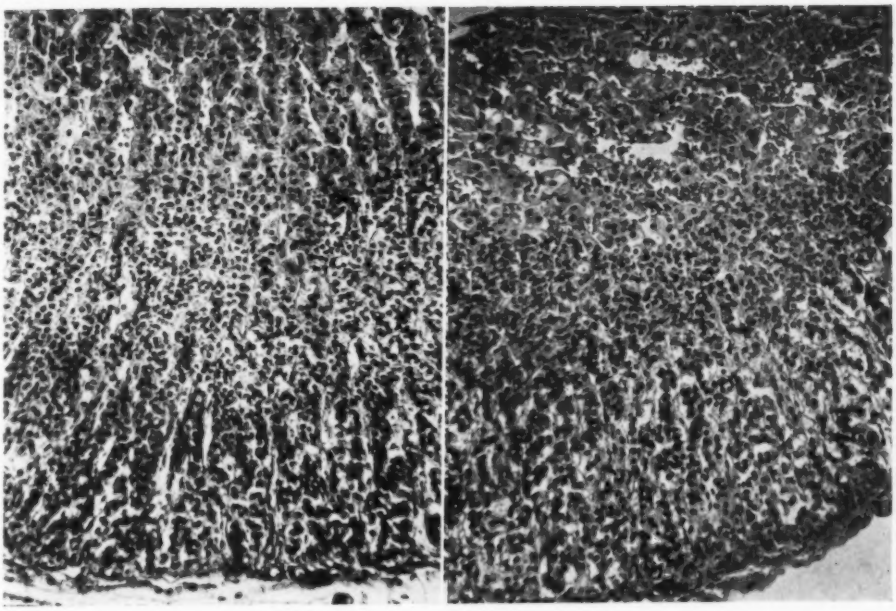
Comparison of testicular structure of hypophysectomized animals[2, 8, 9] and of the patient reported reveals similarity in the reduction of interstitial cells. This was complete in the case reported in contrast to the animal experiments. In the anencephalic monster used for comparison, the interstitial cells were not reduced, but there was the identical increase in connective tissue and sparsity of tubules (Fig. 3). Whether this histology is frequent in male anencephalic monsters requires further investigation.

The thymus gland, as compared to that of the anencephalic monster, was not as large, but larger than would be anticipated in a normal newborn infant. There were no abnormalities of histologic structure in either gland.

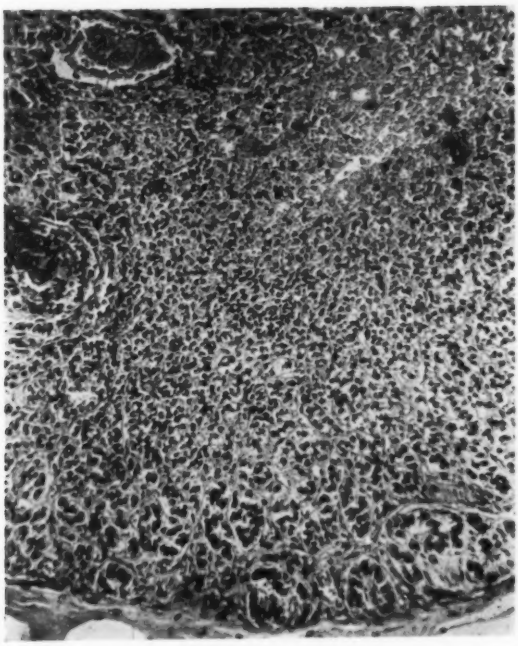
TABLE I

	PITUITARY AND SELLA	ADRENAL	TESTES AND EPIDIDYMIDES	THYMUS	THYROID
Normal	Gross: Sella well formed with clinoids present Microscopic: 3 lobes present	Wt.: 5 grams each Microscopic: Zona glomerulosa and fasciculata poorly differentiated; fetal cortex and medulla prominent; lipoid material scanty and small amount present found in peripheral part of definitive cortex	Wt.: 1 gram each Measurements: 0.5 × 0.5 × 1.0 cm. Microscopic: Connective tissue minimal in amount; large eosinophilic cells found in connective tissue between tubules resembling mature interstitial cells; rete testes and epididymides well developed	Wt.: 11 grams Microscopic: Lobules small and separated by loose connective tissue; Hassall's corpuscles few in number	Wt.: 1.5-5.0 grams Microscopic: Acini well formed and contain colloid
Anencephalic monster*	Gross: Sella poorly formed; clinoids not developed; base of sella flat; pituitary hypoplastic Microscopic: All 3 lobes present but hypoplastic; presence of 3 lobes very rare in this condition	Wt.: Right 0.6 gram; left 0.5 gram Microscopic: Zona glomerulosa and fasciculata narrowed; fetal cortex readily identifiable but involuting and markedly contracted as compared to normal; medulla not identified; fetal cortex more prominent and medulla less prominent than that described as typical by Potter; excess lipoid found in definitive cortex	Wt.: 0.6 gram each Microscopic: Connective tissue markedly increased over normal; interstitial cells demonstrable and number not decreased; rete testes and epididymides not unusual	Wt.: 20 grams Microscopic: Normal; not as that described as typical where lobules are large and branching character not visible	Wt.: 1.2 grams Microscopic: Normal
J. H.	Gross: Sella well formed but ½ normal size; diaphragma sellae lay tightly over sella and no opening for an infundibulum present Microscopic: No pituitary tissue demonstrable	Wt.: Right and left combined, less than 1 gram Microscopic: Zona glomerulosa and fasciculata present but very poorly differentiated and narrowed; nodular appearance present throughout definitive cortex; fetal cortex identifiable in only very few sections and the medulla scanty; zona fasciculata had heavy diffuse lipoid of even greater quantity than anencephalic monster	Wt.: Approximately 0.5 gram each Microscopic: Interstitial connective tissue preponderant; interstitial cells not seen; rete testes and epididymides not unusual	Wt.: 16.5 grams Microscopic: Normal	Wt.: 1.0 gram Microscopic: Normal

*Anencephalic cited for comparison is one born shortly after J. H. This infant lived forty-eight hours.

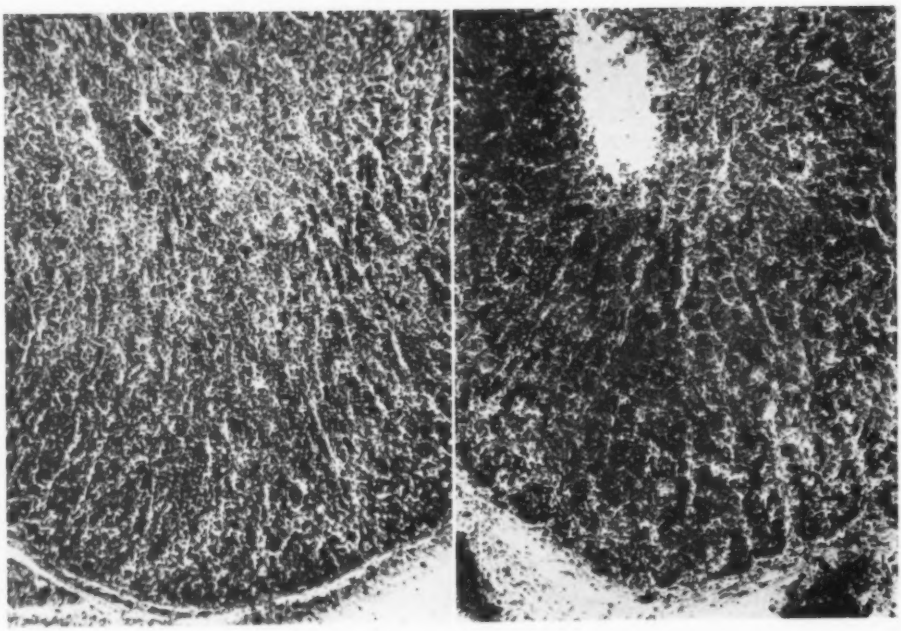


A. *B.*

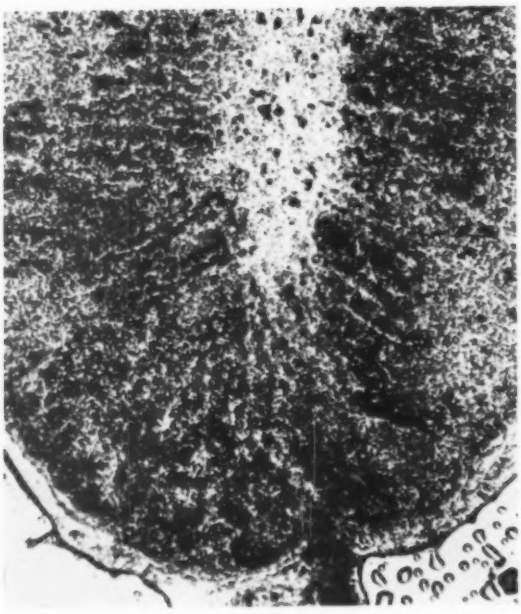


C.

Fig. 1.—*A*, Normal adrenal of newborn infant portraying relatively thick definitive cortex and fetal cortex. *B*, Adrenal of anencephalic monster portraying thinner cortex and outer zones. Some fetal cortex persists although unusual in these monsters. *C*, Adrenal of J. H., demonstrating absence of fetal cortex, poor organization of permanent cortex, and nodular appearance. (Hematoxylin and eosin stain; ×120; reduced ¼.)

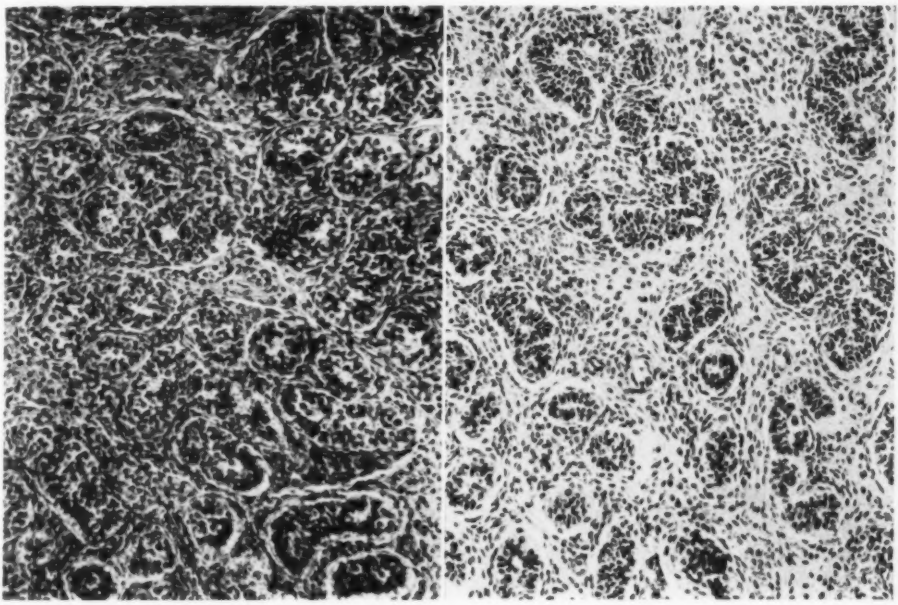


A. *B.*

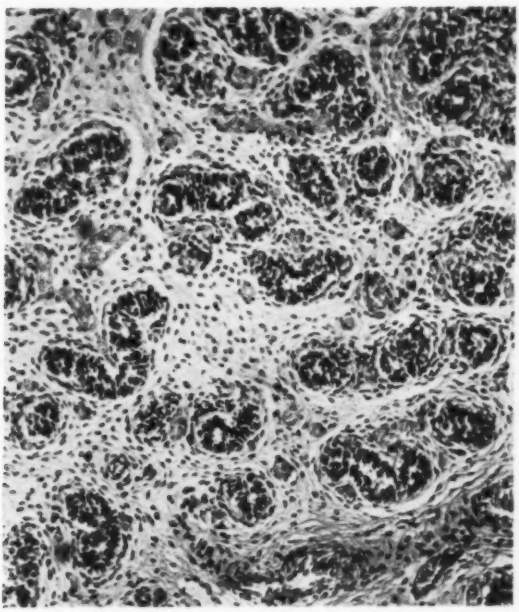


C.

Fig. 2.—*A*, Normal adrenal with minimal amount of lipoid in cortex. *B*, Anencephalic adrenal with moderate amount of lipoid in cortex. *C*, Adrenal of J. H. with excessive lipoid in cortex. (Fat stain; ×75; reduced ¼.)



A. *B.*



C.

Fig. 3.—*A*, Testis of normal newborn infant with scanty connective tissue. *B*, Testis of anencephalic monster with excessive connective tissue. *C*, Testis of J. H. with same preponderance of connective tissue. (Hematoxylin and eosin stain; ×120; reduced ¼.)

No pathology of the thyroid was demonstrated which is consistent with the findings in both the hypophysectomized fetus and in anencephaly.[12]

There seems to be little doubt that the hypoplasia of the adrenals and testes of the patient reported was due to hypopituitarism. Having established hypopituitarism, both pathologically by absence of the gland and by contrast of the peripheral endocrine glands with hypopituitary animal and human fetuses, the etiology of the hypopituitarism may be considered, although with present knowledge it is difficult to determine the etiology. The causes of the pituitary deficiency to be considered are as follows: (1) a normal pituitary originally may have occupied its anatomic place in the sella but was destroyed in later fetal life, possibly because of failure of normal blood supply to be established, (2) a pituitary gland never developed, and (3) a hypoplastic and functionally deficient gland was aberrantly located.

One might expect that if Rathke's pouch had failed to develop in the normal position, the bony sella would not have been formed normally.[19, 20] In support of this is that anencephalic monsters who have malformed pituitary glands from early embryologic development have malformed sellae.[1, 12] Development of a normal sella, however, may not be completely dependent on the initial presence of pituitary tissue in that area, as the course of bone development and the assumption of characteristic form by different bone are inherent and determined through gene action.[21] Arey[21, 22] exemplifies this by stating that a graft of a suitable piece of early limb bud of chick embryo transplanted on to the chorioallantoic membrane differentiates into femur.

The concept that the pituitary gland never formed is hardly tenable in view of Jost's work determining sexual differentiation following hypophysectomy. If the cause and effect of hypophysectomy in the rabbit fetus can be applied to the human being—and there is evidence that the rabbit and human being follow the same embryologic developmental pattern, as Grumbach and associates[23] have shown that absence of gonads in the human fetus causes a female type of sex differentiation which Jost[1] has shown also to be true in rabbits castrated in early fetal life—this infant should not have developed even hypoplastic male external genitalia if there was complete absence of the pituitary. If the hypothesis is correct that the pituitary must be present for development of male external genitalia, it must be qualified by stating that a hypoplastic anterior lobe such as is found in anencephalic monsters is sufficient to supply the stimulus for sex differentiation.

As the area between the posterior pharynx and the sella was not examined, the possibility of a hypoplastic aberrant gland cannot be excluded. Such a gland could account for sexual differentiation, hypoadrenalism, and hypogonadism but possibly not for normal formation of the sella.

SUMMARY

A case is presented of a normal-appearing newborn infant except for small genitalia and cryptorchidism who apparently had no pituitary gland, and had secondary anatomic

hypoplasia of the adrenal glands and testes.

The case reported has many histologic features in common with both anencephalic monsters and some species of animals decapitated in utero that are subsequently brought to term: (1) the patient had no pituitary gland demonstrable, although the possibility that an aberrant gland may have been present cannot be disproved; (2) the adrenal glands were hypoplastic and had fat-staining qualities similar to those found in the adrenal glands of anencephalic monsters; (3) the thymus gland was moderately enlarged; (4) the thyroid was histologically and quantitatively normal; (5) the pancreas was grossly normal; and (6) the testes of the anencephalic monster and of the case reported were identical in the extensive increases in connective tissue, although such an increase has not previously been reported in anencephalic monsters or hypopituitary animal fetuses.

Thorough investigation of the pituitary and hypothalamus is indicated in future cases of infants with adrenal insufficiency, hypogonadism, or incomplete external genital development dying in the newborn period. Further investigation of the endocrine glands and hypothalamus of anencephalic monsters is also indicated. Studies of this type may be of further benefit in understanding fetal endocrinology.

We are deeply indebted to Dr. Edith Potter, Pathologist, Chicago Lying-In Hospital, Chicago, Ill., for an extensive review of the endocrine slides; Dr. D. Murray Angevine, Professor of Pathology, University of Wisconsin; Dr. L. Brainerd Arey, Professor of Anatomy, Northwestern University, Chicago, Ill.; Dr. Lawson Wilkins, Associate Professor of Pediatrics, Johns Hopkins University, Baltimore, Md.; and Drs. Robert Dunn and John Green, Pathologists, Iowa Methodist Hospital, Des Moines, Iowa, for also reviewing the slides.

In addition we are indebted to Dr. Lawson Wilkins for his review and suggestions pertaining to the manuscript.

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First printed account of epidemic meningitis in America by L. Danielson and E. Mann

Without any apparent predisposition, the patient is suddenly taken with violent pain in the head and stomach, succeeded by cold chills, and followed by nausea and puking; matter discharged from the stomach of no unusual or morbid appearance; respirations short and laborious; tongue a little white toward the root, and moist; velocity of the blood increased, with a sensible diminution of the momentum in the radical, while in the carotid arteries it was much augmented; and in a child of 15 months old, a very violent pulsation was discovered, at the fontanel (opening of the head;) the eyes have a wild vacant stare, without much if any appearance of inflammation; the heat of the skin soon becomes much increased, yet the skin is remarkably dry: these symptoms are accompanied by a peculiar fearfulness, as if in danger of falling from the bed or nurse's arms, and continue from six to nine hours, when coma (suppression of sense and voluntary motion) commences, with increasing debility; extremities become cold; livid spots, resembling petechiae (purple spots which appear in the last stages of certain fevers,) appear under the skin, on the face, neck, and extremities; pulse small, irregular, and unequal; spasms occur at intervals, which increase in violence and frequency in proportion as the force of the circulation decreases; at this time the eyes appear glassy, and the size of the pupil varies suddenly, from almost wholly obliterating the iris, down to the size of a millet seed, and then again as suddenly dilating. These symptoms seem to mark the second period of the disease, and continue from three to five hours. The third and last stage is distinguished by a total loss of pulsation at the wrists; livid appearances become more general; spasms more violent; coma more profound; death!

From THE MEDICAL AND AGRICULTURAL REGISTER, May, 1806.

MECONIUM PERITONITIS: A SURGICAL EMERGENCY

A Brief Review of Surgical Survivals and a Case Report

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MECONIUM peritonitis is a sterile chemical and foreign body reaction resulting from leakage of bowel content into the peritoneal cavity during the late intrauterine or early neonatal period. Within twenty-four hours of birth the meconium may become contaminated with various organisms and the meconium peritonitis converted to a bacterial one.

In 1838 Simpson[8] first presented a comprehensive discussion of the subject of meconium peritonitis and listed twenty-five cases that he had found in the literature. Low and associates[8] in 1949 found more than one hundred reported cases. The vast majority were proved at autopsy. Bendel and Michel[1] found three cases in 108,744 live births from 1937 to July of 1952 at Charity Hospital, New Orleans, which would seem to indicate that the condition of meconium peritonitis is relatively infrequent.

Surgical survivals are unusual. Agerty and associates[1] reported the first in 1943. Bendel and Michel reviewed the literature in 1952 and found eight cases to which they added one of their own. Additional cases with survival after surgery have been reported by Franklin and Hosford[7] (two cases) in 1952, Forshall and associates[1] in 1952, Bentley and Waterson[2] (two cases) in 1954, Nixon[12] (two cases) in 1954, and Brunkow and coworkers[3] in 1949, making a total of eighteen cases including the present case report. Eight additional patients were operated upon with fatal results. One additional patient survived without operation and at the age of 2½ months had surgical biopsy following an x-ray diagnosis of meconium peritonitis.[13] The average age at the time of surgery was 2 days.

CASE REPORT

G. D. F., a white male infant weighing 7 pounds 11 ounces, born March 28, 1952, of an uneventful delivery, was the fourth pregnancy of a 36-year-old mother. Forty-eight hours after birth it was noted that the abdomen was distended and at the same time it was noted that the anus was imperforate. A thin bulging discolored membrane (Ladd and Gross type 2) was readily visualized. The abdominal distention was considered to be due to the anal obstruction. The membrane was opened and dilated. Meconium of a greenish-black color began to pass freely and in a continuous flow. The infant was observed for twenty-four hours, after which time he began to vomit bile-stained fluid. The distention was no less than when first observed. Peristalsis could be seen through the anterior abdominal wall. An abdominal roentgenogram was taken which showed "a large pneumoperitoneum and some gas scattered throughout the intestinal tract. The pneumoperitoneum made the bowel walls visible and they appear thickened, in-

dicating probable peritoneal exudate." A diagnosis of perforated bowel with meconium peritonitis was made and the infant was prepared for surgery with intravenous fluids, gastric suction, 200,000 units of procaine penicillin and ½ Gm. of dihydrostreptomycin intramuscularly.

Under open drop ether, a left pararectus incision was made from the symphysis to 2 cm. above the umbilicus. The peritoneum was opened, air escaped freely. The visceral and parietal peritoneal surfaces were matted with a green mixture of meconium and fibrin, and the intestines were matted together with soft fibrinous adhesions. The sigmoid colon was plastered against the bladder and upon freeing this, a 1 cm. rent (sealed by fibrinous exudate) was found on the anterior aspect of the sigmoid. Early gangrenous changes were seen throughout the entire sigmoid. The hole was repaired with 3-0 chromic intestinal suture. The remainder of the bowel was explored for anomalies but none were found. A loop colostomy was then brought out through a left lower quadrant muscle-splitting incision. The exploratory incision was then closed.

A culture of the peritoneal fluid grew out hemolytic *Staphylococcus aureus.*

Fig. 1.—Preoperative picture of an infant aged 36 hours, showing thermometer in rectum, pneumoperitoneum, and thickened walls of small bowel.

The postoperative course was stormy. The colostomy began to function in forty-eight hours; small oral feedings were retained after four days; oxygen was necessary for four days; the white blood count remained over 17,000 for fifteen days. Oral feedings were not taken eagerly until about the nineteenth day. The infant was discharged well (except for the colostomy) twenty-two days after the operation. Weight was 8 pounds 2½ ounces.

Rectal dilatations were done regularly for the next nine months, which brought the anus to normal. At age 9 months the colostomy was closed. The postoperative course was uneventful. The anus began to function normally, and the baby was discharged on the eighth day.

Examination of the baby at 3 years of age showed a normal healthy child. Bowel movements were normal. Barium studies of the rectosigmoid showed no narrowing at the area of perforation and repair.

in the bowel). A few cases have been reported where there was no obstruction and no perforation (the perforation was probably sealed). One surgical survival (Franklin and Hosford's Case 2) was proved to be a perforation due to meconium ileus with an associated pancreatic fibrosis. The meconium in such cases becomes an obstructing puttylike mass.

The diagnosis depends upon careful examination of the newborn infant.

TABLE I. INFANTS SURVIVING SURGERY FOR MECONIUM PERITONITIS

	YEAR	OBSTRUCTION	PERFORATION	BACTERIA	CALCIUM ON X-RAY
1. Agerty, Ziserman	1943	None	Distal ileum	None	None
2. Neuhauser	1944	Atresia jejunum	None	None	Positive
3. Low and associates	1949	Atresia ileum	Ileum	None	Positive
4. Brunkow and associates	1949	None	Not found	*Staph. albus* Nonhem. strep. *Esch. coli*	Positive
5. MacMillan and Lee	1950	Splenic flex colon	Cecum	Hem. *Staph. aureus*	Neg.
6. Conrad and Robbins	1951	Atresia jejunum	Jejunum	None	Positive
7. Packard and Reynolds	1951	None	Not found	None	Neg.
8. Doyle	1951	Incarcerated hernia	Ascending colon	*Aerobacter aerogenes*	Positive
9. Doyle	1951	None	Ileum	None	Not taken
10. Franklin and Hosford	1952(a)	None	Yes—exact site unknown	None	Positive
11. Franklin and Hosford	1952(b)	Meconium ileus	Yes	None	Positive
12. Forshall and associates	1952	----------	----------	----------	--------
13. Bendel and associates	1953	None found	Ileum	None	Positive
14. Bentley	1954	Volvulus	Ileum	Coagulase neg. staph.	Neg.
15. Bentley	1954	Atresia	Yes	None	Positive
16. Nixon	1954	Atresia	Yes	None	Neg.
17. Nixon	1954	Atresia	Yes	None	Positive
18. White	1955	Imperf. anus	Sigmoid	Hem. *Staph. aureus*	Neg.

DISCUSSION

Perforation of the intestine with resultant meconium peritonitis may occur in the following manner: (1) congenital obstruction with perforation; (2) acquired obstruction with perforation; (3) traumatic perforation without obstruction; (4) spontaneous perforation (localized defects

The most common first sign was abdominal distention. This was either associated with or soon followed by vomiting, mild cyanosis, listlessness, and feeble cry. Later the veins of the abdomen become prominent, peristalsis may be absent or so hyperactive as to be visible beneath the abdominal skin. The abdomen is usually tym-

panitic. Distention, if not present at birth, will usually be visible in the first twenty-four hours.

Roentgen study of the abdomen in nearly 75 per cent of twenty-one instances showed a pathognomonic picture. Neuhauser[11] has emphasized that no other condition produces the one or more irregular shadows of calcific density lying either within the bowel lumen, within the bowel wall, or lying loosely adherent to the peritoneal surface of the bowel or parietes.

The treatment of meconium peritonitis is immediate surgery with the object of stopping the leak of meconium from the bowel and removing obstructing factors.

Every effort should be made to restore and maintain the infant in electrolytic balance, decompress the stomach by indwelling catheter, and cover with antibiotics of broad spectrum type. Blood should be available for transfusion. An examination of the entire bowel should be made for possible atresia, stenosis, or multiple obstructing lesions. Postoperative care demands a great deal of patience, attention, and supportive care. Where there is atresia or stenosis, resection and anastomosis must be done. The mortality in cases of this type is still quite high.

SUMMARY

1. A review of the literature shows that while meconium peritonitis is uncommon, it is almost uniformly fatal without surgical treatment.

2. Surgical treatment offers a good chance for survival, as it has been shown that the peritonitis is due to perforation of the intestine, resulting usually from a congenital intestinal obstruction.

3. A case report of surgical treatment with survival has been presented.

I wish to acknowledge the great help and encouragement of Dr. Morton Schaffran in diagnosis and treatment in this case and the assistance of Dr. John Marks in prolonged postoperative care.

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ARTHROGRYPOSIS MULTIPLEX CONGENITA

Case Report

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IN REVIEWING the literature, we have noted that only eighty-one cases of this rare disease have been reported. The first report was made in 1841 by Otto who described the condition as a congenital myodystrophy. Otto's report was followed by reports from E. Rosenberg in 1905 who collected fifty-six cases and termed them "arthrogryposis multiplex congenita"; Stern[8] in 1923 reported a single case, and in 1925 Lewin[4] also reported a single case. In 1932, using the term "amyoplasia congenita," Sheldon[7] described one patient afflicted with this disease. Middleton[5] in 1934 reported a case using the term "myodystrophia foetalis deformans." Katzeff[3] in 1943 reported observations on eighteen patients with this disease seen at Children's Hospital in Boston from 1925 to 1942. In 1947 Steindler[9] discussed the pathological findings and the therapy in an address before the International College of Surgeons. Hillman and Johnson[2] reported a study of two sets of identical twins in 1952, in which one child of each pair was afflicted with classical arthrogryposis multiplex congenita and the other twin was normal.

Arthrogryposis is a rare disease characterized by limitation of motion of the joints of the extremities involved. The disease is present at birth and is nonprogressive in character. The disorder appears sporadically. It occurs about five times as frequently in males as in females. It does not appear to be hereditary or familial and may be associated with other deformities, i.e., clubfeet, clubhands, and congenital dislocations. There have been many theories advanced as to the etiology of this disease, but none have been proved as the true etiological factor. Compression in utero has been advanced as the condition leading to the development of the disease but there is no conclusive evidence that this is true. Stern[8] believed that the basic factor was the thickening of the periarticular structures, while Middleton[5] concluded that "the deformity resulted from a fatty degeneration of the limb muscles occurring during late intrauterine life," and that it was analogous to muscular dystrophy occurring in the adult. Badgely[1] felt that the characteristic deformities of this illness were indications of the arrest of muscle development and consequent failure of rotation of the limbs that normally occurs during the third fetal month.

The principal pathological changes of this disease involve the striated muscle fibers which show atrophy,

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fatty replacement and infiltration, and the articular capsules which are thickened and inelastic. Degeneration of the anterior and posterior horn cells have been reported, but the relationship of the involvement of the spinal cord to the lesions in and about the joints has not been established.

Clinically, there is little palpable muscle tissue and the structures overlying the joints seem thickened and contracted. When the arms are involved they are rotated inward and involvement of the thighs causes an outward rotation of the part. The elbows and knees appear cylindrical and are usually ankylosed in extension, although fixation of the knees in flexion may occur. The wrists and fingers are fixed in acute flexion and clubfeet are present in this illness.

X-ray studies in infants and younger children show deficient muscle shadows with increased density of the capsular areas; but no bony changes are evident. In older children, x-ray reveals secondary bony changes due to the long-standing contractures of the soft tissues.

Therapy in this illness consists of manipulations of the involved parts, with or without anesthesia, supports, such as splints and braces, and surgical correction of deformity.

We wish to present a case of arthrogryposis multiplex congenita combined with an apparent Klippel-Feil syndrome.

CASE REPORT

A. E. B. was delivered at St. Vincent's Hospital, Philadelphia, on Oct. 6, 1955, via the normal vaginal route, spontaneously, as a frank breech presentation. She cried immediately and resuscitation was not necessary. Birth weight was 4 pounds 15 ounces; length from heel to crown was 17 inches; head circumference was 12¾ inches and chest circumference was 11 inches. When the infant was examined, approximately five hours after birth, a classical picture of arthrogryposis multiplex congenita was noted. It was noted that very little muscle tissue was palpable in the arms and legs of the infant and that, in general, the muscle tone was poor. The neck was very short and a web extending from the stylous process of the temporal bone to the shoulder was present bilaterally. The hair line was lower than usual, extending well onto the neck, actually presenting the gross appearance of the Klippel-Feil syndrome, although this diagnosis was not substantiated by the x-ray films. Involvement of the upper extremities included limited range of motion of shoulders, flexion of the

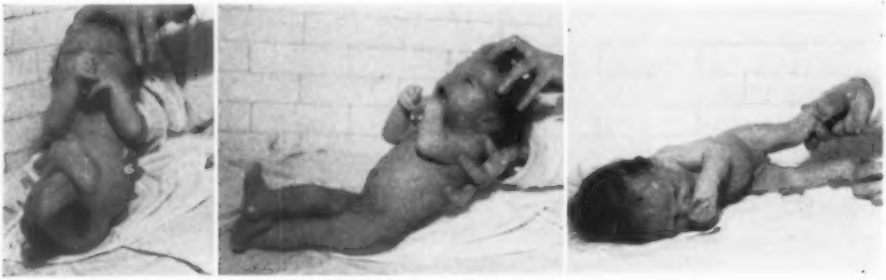

Fig. 1.

elbows, and the third and fourth fingers of both hands were in acute palmar flexion. Neither the elbows nor fingers involved could be extended. The hips were flexed so that the feet remained near the face and the knees were extended. It was impossible to extend the hips or flex the knees during the initial examination, but twenty-four hours later we were able to extend the hips to a 90 degree angle with trunk of the body. The hip joints appeared subluxated; both lower legs were rotated outwardly. The feet were in a talipes calcaneus position.

X-ray films of the bones revealed no bony abnormalities. In contrast to a true Klippel-Feil syndrome, the cervical vertebrae were separate and distinct and were seven in number. There appeared to be very little muscle shadow present in the extremities and increased densities were noted over the joint capsules.

A. E. B.'s mother was a 34-year-old para ii, gravida i, Caucasian who had adequate prenatal care. She experienced no unusual occurrences during her pregnancy. There were no known exposures to rubella, irradiation, or other noxious agents during her pregnancy. Her first pregnancy resulted in a living normal infant, weighing 6 pounds 5 ounces. The family history was noncontributory.

Therapy, thus far, has consisted of gentle manipulation of the involved parts in the opposite direction to the deformity. Attempts have been made to extend the fingers by placing a small cotton ball in the palms of the hands periodically.

The infant has progressed well, weighing 6 pounds 2½ ounces on Nov. 16, 1955. She takes her formula well and seems alert and normal in all respects except for the deformities described.

She is to be transferred to the Du-Pont Institute in Wilmington, Delaware, for further treatment.

SUMMARY

A brief review of the literature concerning arthrogryposis multiplex congenita has been presented, with a report of a case diagnosed at birth and associated with a shortened webbed neck suggestive of Klippel-Feil syndrome, although the cervical vertebrae were not fused.

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Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

A 2-day-old premature infant girl was admitted to the hospital because of purpura and jaundice.

The father was living and well. The mother, 22 years of age, had been well prior to pregnancy; there had been no previous pregnancies. During her pregnancy, the mother had occasional "boils," and for the last two months had noted swelling of her hands and feet, and bleeding of her gums when she brushed her teeth. Her blood pressure was normal. She had no known fevers. The father and mother are Rh-positive. There was no family history of tuberculosis, kidney disease, allergy, or venereal disease. A maternal grandmother had diabetes. The patient was born two days before admission after an 8-month normal pregnancy and a 6-hour labor; the weight was 4 pounds 9 ounces.

The baby was noted to have generalized purpuric spots, particularly on the back. There was some difficulty with respiration but no cyanosis. The patient was fed by a Breck feeder prior to admission here. Thirty-six hours after delivery, jaundice was noted and more purpuric spots appeared. The liver and spleen were noted to be enlarged, and the temperature was 102° F. (rectal). There had been no convulsions, hemorrhages, or weakness. The patient had received vitamin K and ascorbic acid on the day before admission.

Physical examination on admission disclosed a temperature of 96° F., pulse 100, respirations 28, and body weight 4 pounds 9 ounces. The child was small but well developed; she appeared acutely ill and had a sharp cry. The skin was moderately icteric. Over the trunk, extremities, and head were multiple, small (1 to 2 mm. in diameter), petechial spots and occasional purpuric spots up to 0.5 cm. in diameter.

The patient was Group O, Rh-positive and probably heterozygous. The Coombs test was negative. The urine examination revealed 2+ albumin and a 4+ test for bile. The initial hemoglobin level was 17 grams, the erythrocyte count was 5.1 million per cubic millimeter, the leukocytes numbered 8,000 per cubic millimeter. The differential leukocyte count revealed 30 per cent polymorphonuclear cells, 70 per cent mononuclear cells, with 18,000 nucleated red blood cells per cubic millimeter. The platelet count was 7,000

per cubic millimeter and the platelets appeared to be decreased on the film. The cerebrospinal fluid was xanthochromic with a 1+ Pandy reaction and normal sugar values; it contained 990 crenated erythrocytes per cubic millimeter, 90 leukocytes per cubic millimeter, of which 30 per cent were polymorphonuclear cells and 60 per cent monocytes. The culture of the cerebrospinal fluid was sterile. A micro-Hinton examination of the blood was negative. A smear of one of the petechial spots on the skin revealed no organisms. The prothrombin time on admission was 16 seconds against a control of 18 seconds. A spread of the mother's blood revealed that she had adequate platelets.

On entry the infant was given vitamin K, streptomycin, penicillin, and sulfadiazine in adequate doses. The antibiotics were continued, and the infant was fed by gavage tube after the second hospital day. Then vitamins C and D were added to the regimen. The infant became more icteric over the first week in the hospital, but otherwise remained in about the same condition. No new petechial areas appeared, and the purpuric spots present on entry gradually resolved.

The platelets in the peripheral blood remained decreased throughout the hospital course, averaging 6,000 per cubic millimeter and rising to 55,000 per cubic millimeter one day before death. The peripheral leukocyte count remained between 8,000 and 18,000 per cubic millimeter, with a shift to the left in the polymorphonuclear leukocyte count. The percentage of mononuclear cells in the peripheral blood remained persistently high, at about 15 per cent. Nucleated erythrocytes remained in the peripheral blood at all times, ranging from 4 to 40 nucleated erythrocytes per hundred leukocytes. Four throat cultures, taken over her hospital course, all showed a heavy growth of *Pseudomonas aeruginosa.*

The patient's condition began to improve after the first week. The icterus began to subside. The antibiotics were gradually withdrawn. A roentgenogram of the skull and chest was read as normal. A roentgenogram of the abdomen showed enlargement of the liver and spleen, without calcification. The long bones showed moderate osteosclerosis of the new bone, but no other evident abnormality. Attempts at tibial marrow aspiration were unsuccessful, as the bone could not be penetrated by the needle. The infant continued to do very well. Her weight became stabilized on the gavage feedings between 4 pounds 2 ounces and 4 pounds 4 ounces. The hemoglobin of the peripheral blood remained at the entry level of 17 to 18 grams per cent.

On the day prior to death, the infant was thought to look much better. The purpura and jaundice had completely cleared. The platelet count had risen to 55,000 per cubic millimeter. At 2:20 A.M. the following morning, however, the infant suddenly became acutely ill. During the next few minutes she began to pour forth large amounts of fresh blood from both mouth and nose, and she died.

DISCUSSION

DR. FRED ALLEN.*—This is the case of a small female infant, born at about 8 months' gestation, weighing 4 pounds 9 ounces. She was admitted to the Children's Hospital at the age of 2

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days with purpura, jaundice, enlargement of the liver and spleen, and deficiency of platelets as the most striking findings. Quite obviously the diagnosis to make in such a situation is erythroblastosis fetalis; not only is that by far the most common cause of such a syndrome, the diagnosis of which is very simple to confirm, but it is about the only disease that can cause this kind of clinical picture, for which there is a readily available and very effective treatment. I am sure, therefore, that that was the initial diagnosis and that prompt steps were made to confirm it. However, in discussing this case, I should like to consider other possibilities first, and then come back to the question of erythroblastosis fetalis.

We can make, if we wish, a sort of general diagnosis of congenital thrombocytopenic purpura in this baby; that is obviously what she had, and consider the various things that may cause it. Leukemia and aplastic anemia may obviously be causes of thrombocytopenic purpura. It is equally obvious that this baby had neither of these diseases, for she did not have anemia at any time. There are a number of infectious diseases that may cause thrombocytopenic purpura, as tuberculosis and meningococcus septicemia. These are not transmitted through the placenta to the fetus, so that we can rule out any bacterial infection in the fetus as a cause of her trouble. Syphilis certainly may produce this exact clinical picture. We have the presumption that the mother had a negative Hinton test during pregnancy, because of the Massachusetts state law requiring Hinton tests on all pregnant women. We have the information in the protocol that the baby had a negative Hinton test after admission. It is conceivable that the mother developed syphilis at some time subsequent to her Hinton test. It is conceivable also that the baby had syphilis in spite of a negative Hinton test. I called the State Department of Laboratories yesterday and learned that in doing the micro-Hinton tests they now use equal parts of serum and antigen. We know from past experience that occasionally in congenital syphilis one may have a negative Hinton test under such conditions, and a positive test when a smaller quantity of serum or dilution of the serum is used to overcome the prozone effect occasionally seen in babies with congenital syphilis. It does not seem very likely, however, that one would have such a rare combination of circumstances, and I would therefore not seriously consider the diagnosis of syphilis. Thrombocytopenic purpura may be caused by a variety of drugs, notably heavy metals, quinidine, and digitoxin. There is no evidence that the mother received any such drugs during pregnancy. We are told that she was taking pills of some sort for gall bladder trouble for a year. I do not think we can be certain that she did not receive some drug that would produce thrombocytopenia; but I think it rather unlikely. Furthermore, the mother did not have thrombocytopenia. I would therefore think that drugs as a cause of this syndrome are extremely unlikely.

We then come to a group of diseases that are caused by antibodies formed by the mother and passively transferred to the fetus. The first of these to consider are antiplatelet antibodies. The ordinary case of idiopathic thrombocytopenic purpura is one in which antiplatelet antibodies can be demon-

strated in the patient. These antibodies cause agglutination of their own platelets, as well as those of all other people. There are a number of recorded cases in which such antibodies, which have produced thrombopenic purpura in the mother, have passed through the placenta, presumably, to attack the platelets of the fetus, and produce thrombocytopenic purpura in the fetus. Perhaps we should not call this an antibody, but it acts as an antibody generally acts, in the sense that it does cause agglutination of the platelets. Here, of course, the mother did not have thrombocytopenic purpura, so we cannot make that particular diagnosis. There are a number of cases recorded also in which the mother had plenty of platelet antibodies in her serum, which caused in vitro clumping of her own platelets and which caused an actual thrombocytopenia in the infant. This is a possible explanation of this picture, although there are other things which seem to be incompatible with such a diagnosis, including the enlargement of the liver and spleen. Such a disease caused by platelet antibodies is ordinarily self-limited; the baby recovers quite rapidly within two or three weeks, and is normal again.

The other disease caused by antibodies is, of course, erythroblastosis fetalis, and it is perfectly obvious that the enlarged liver and spleen, the jaundice, the petechial hemorrhages, the purpura, that is, the low platelets, and the presence in the circulating blood of quite large numbers of nucleated blood cells are all suggestive of that diagnosis. There are a few points against the diagnosis, however; one of them, not very important, is that this baby had petechial hemorrhages or purpura at the time of birth, which is something that I have not seen in erythroblastosis fetalis, although I would assume it might occur occasionally. In erythroblastosis, the purpura, if it develops, and it does so frequently, comes after birth and may develop within the first half hour after birth. We all know, of course, that when something develops that quickly one will frequently make the somewhat misleading statement that it was present from birth. Another great stumbling block in making a diagnosis of erythroblastosis is the fact that this baby had a negative Coombs test and was group O. This absolutely rules out erythroblastosis in my opinion. Furthermore, we have the information that both baby and mother are Rh-positive. Then there is the question of kernicterus, which naturally comes up when one thinks of erythroblastosis. This baby was not only quite jaundiced when she was admitted but the jaundice increased in severity throughout the first week of life, or perhaps longer. We have come to realize that erythroblastosis is not the only disease or condition in which kernicterus may occur, and we now believe that in any condition in which in the newborn period there is severe jaundice, there may be kernicterus. Simple prematurity and the physiologic icterus that one gets in normal babies may combine to produce a very severe jaundice that results in kernicterus, and in fact any condition that produces jaundice can be thought of in that way. I would not, therefore, be surprised if this baby had kernicterus, and I think that, if so, it is rather an incidental finding.

The mother had a history of bleeding gums. The baby had purpura. One thinks of a vitamin deficiency, particularly vitamin C deficiency. This in-

fant almost surely does not have scurvy. Low platelets ordinarily are not a part of scurvy, if ever.

We next come to a group of infectious diseases, not bacterial, which may be transmitted from the mother to the fetus in utero, and which may produce this sort of clinical picture at birth. We are told in the history that the baby had fever; as I recall the temperature before admission was charted at 102° F.; after admission, 96° F. The baby also was described as being acutely ill, and, most important of all, in the spinal fluid there was an abnormal finding of 90 white cells per cubic millimeter, 30 of which were polymorphonuclear leukocytes. That cannot be explained by the small number of crenated red cells which were found in the spinal fluid at the same time. The other findings in the spinal fluid of note were xanthochromia, which may occur in normal infants, but may be suggestive of something else in this disease, and a 1 plus Pandy reaction, which indicates some increase in the spinal fluid globulin. The first disease we think of, which we have known about for some time, and which may cause all these findings, is toxoplasmosis. When toxoplasmosis occurs as congenital disease, it almost always occurs when the mother has no history of difficulty, which is true in this case. Purpura, hepatosplenomegaly, jaundice, central nervous system symptoms, are all quite characteristic of toxoplasmosis. In toxoplasmosis we are accustomed to see minute calcifications in the brain that show up by x-ray. These were absent in this baby, but I do not believe that rules out the diagnosis of toxoplasmosis, provided the lesion had not been present long enough to allow calcification to occur. We lack also in this case any information as to whether there were lesions in the choroid and retina. In toxoplasmosis, chorioretinitis is one of the constant and useful diagnostic features of the disease. Whether these were absent in the baby or whether they were not looked for is not indicated by the protocol, and if we are willing to make the assumption that the eyegrounds were not examined we can still make a presumptive diagnosis of toxoplasmosis.

There is another condition, namely, torulosis, which we have always considered as a possible differential diagnosis in erythroblastosis fetalis. I have not been able to find any case report that describes torulosis in the newborn infant, although I think there are some. It seems to me there was a case back about 1947 that Dr. Farber admitted to the private ward, in which that diagnosis was made, and in which the clinical picture was similar to this. Perhaps against the diagnosis of torulosis is the absence of finding the organisms in the spinal fluid examination. I would rather think that torulosis is not the diagnosis.

Finally, we come to a condition, which is going to be my guess as the diagnosis in this case, which is variously called fetal erythroblastosis inclusion disease, generalized salivary gland virus infection, inclusion body disease, giant cell inclusion disease, and perhaps most recently, generalized cytomegalic inclusion disease. This condition, presumably caused by a virus, although no virus has been isolated that I know of, has caused cases which are to all practical purposes identical with this one. The one with which I personally have had something to do is a case that was sent to us as a consultation by Dr. Walter Hart of

Florence, South Carolina, who wanted us to rule out the diagnosis of erythroblastosis fetalis, and who sent along with the bloods of the mother, baby, and father, some sections of tissues from the baby after he died. We found no evidence of erythroblastosis on serologic examination. The pathologic examination showed typical cells of this inclusion disease in the tubular cells of the kidney. I cannot remember whether there were some intranuclear inclusion bodies. From a brief look at some of the literature I find that there may be nuclear as well as cytoplasmic inclusion bodies. Another note that I found in the literature, in a case reported by Mercer and associates,[1] was that in these cases the bones, the cortex of the femur, the tibia, and the iliac crest were very hard and difficult to penetrate in attempting to do bone marrow studies. A similar note was made in this chart when an attempt was made to aspirate tibial marrow. The x-rays in this case of Mercer showed sclerosis of the shafts of the bone, with diminished density at the ends. Perhaps Dr. Neuhauser will straighten me out on that. Mercer was the first one that I know of to point out that the diagnosis may be made in the clinical case by examination of the urine and looking for these large desquamated cells of tubular epithelium in the urine, very large cells with inclusion bodies. Anemia has been described as quite characteristic of this condition. We found no anemia in this baby. The hemoglobin remained at about 17 grams. Nevertheless, there was evidence of rapid blood formation in the way of numerous nucleated red cells in the peripheral blood at all times during her hospital stay. Lesions have been found in the eyes, the brain, the kidney, the liver, the pancreas, the thyroid gland, and probably in some other tissues. It is characteristic often that the infants are premature, that jaundice develops early, and that they have thrombocytopenia and purpura. Hematemesis was a condition that occurred just prior to death in several of the cases that I read, and in this baby, too, hematemesis seems to have been the event that immediately preceded death. I was not able to learn from the case reports what anyone considered as being the cause of the hematemesis. Neither did I understand from the literature what anyone considered to be the cause of the enlarged liver and spleen, which were universally seen. In a review of the literature by Wyatt and co-workers,[2] in 1950, it is stated that between 10 and 30 per cent (30 per cent in some series) of routine post-mortem examinations had demonstrated these abnormal cells in the salivary glands, and in from 1 to 2 per cent of routine autopsies they found these cells in organs other than the salivary glands. The conclusion which he came to was that this was not an incidental finding of post-mortem examination, as had been heretofore believed, but that the disease characterized by these large cells with inclusion bodies was the actual cause of death.

My first guess for diagnosis will be generalized cytomegalic inclusion disease. I would not be at all surprised if the baby had kernicterus.

DR. FARBER.—Thank you, Dr. Allen. Before you sit down would you review very briefly why you made this last diagnosis?

DR. ALLEN.—Perhaps I should not say I am pretty sure that is the diag-

nosis because I am not. I think toxoplasmosis is an awfully good bet. I think from the clinical findings, which suggest an acute illness, and from the spinal fluid findings, which indicate some infectious process going on in the nervous system, that one of these diseases is the most likely. I have no doubt there are other diseases besides these two that might produce the same sort of clinical findings in this baby. I should think they are perhaps nonspecific in the sense that purpura is not a specific result of a disease; neither is enlargement of the liver or spleen in most cases, nor is jaundice, especially in the newborn period.

DR. FARBER.—Would you review again the reasons for rejection of the diagnosis of erythroblastosis fetalis?

DR. ALLEN.—The serologic diagnosis of erythroblastosis is ordinarily extremely simple. There are two principal groups of erythroblastosis. One is that which gives a positive Coombs test, and the second is a group that gives a negative Coombs test. Those that give a negative Coombs test are, for all practical purposes, and I have never seen an exception, cases in which incompatibility is in the major blood groups, mother ordinarily group O, baby either group A or group B. In this case, the baby is group O, which absolutely rules out erythroblastosis on the basis of ABO incompatibility. The other group with positive Coombs test is largely Rh-erythroblastosis, which is ruled out not only by the negative Coombs test, but by the fact that the mother herself is Rh-positive. At any rate, the negative Coombs test ruled out all that group.

DR. FARBER.—Thank you. What was the house diagnosis in this case?

DR. JOHN HARTMAN.—The house diagnosis was thrombocytopenic purpura, congenital, due to unknown cause; probable pulmonary hemorrhage; hepatosplenomegaly. I think the principal diagnosis offered during the child's life was that of septicemia.

DR. FARBER.—This interesting problem is open for general discussion now, with or without reference to Dr. Allen's interesting suggestions. I was just asked how often one saw sepsis with petechiae at birth, and I do not believe I have ever seen purpuric spots at birth. That makes the most likely diagnosis, in my mind, difficult to relate to sepsis. We are going to ask Dr. Neuhauser to make the diagnosis by showing us the x-ray films.

DR. E. B. D. NEUHAUSER.—We reviewed the films and also what we had written at the time, and apparently we did not think the lungs were normal. We thought that the child probably had a pneumonitis, although it is difficult to say. At least there was irregular density in the lungs, particularly in the right upper lobe, the right base, the aeration was irregular, and on the left side there was a good deal of peripheral emphysema, with bulging of the interspaces. The heart was rather large and globular; it was nonspecific. It is not unusual for normal children to have a heart that big, particularly in the presence of some degree of pulmonary infection. One gets the impression that the liver was quite large, and that there was soft tissue density that could quite well be the spleen.

DR. FARBER.—Did the enlarged liver push the heart up and flatten it out?

DR. NEUHAUSER.—There was a slight transverse lie, yes, that probably in-

creased the prominence of the heart. We re-examined the skull this morning, looking for calcific deposits and could find none, but of course we have overlooked it before, and sometimes the calcific deposits in many of these diseases is too fine to be picked up on the usual x-ray examination in these little babies, most of whom have some faint degree of motion so that it will blur the minute grains of calcific deposit. Unfortunately, of course, that does not make a diagnosis, even if we had seen calcification, because there have been a number of reports now where calcific deposit, similar in appearance and distribution to toxoplasmosis, has been identified in patients with cytomegalic inclusion body disease. So, again, it would not make a diagnosis except to focus our attention to that group of diseases.

There was no evidence of increased intracranial pressure by film, but no specific abnormality that we could detect. The long bones were quite striking in that they were really very dense. The major density was in the diaphysis but also involved the spongiosa at the ends of the bone. There was not too much visible marrow cavity, and the cortex was thick in relation to the width of the marrow cavity, particularly in the tibia, which I imagine was the site where the needle puncture was attempted. The ends of the bone were relatively less dense; they were not abnormally radiolucent. This was not a specific picture at all. We see it in many a newborn premature infant, and it has therefore been called osteosclerosis of the newborn. It has also been reported from Boston as a frequent finding in patients with erythroblastosis that is so severe that they die either in utero or shortly after delivery. We have never accepted that as a significant finding, nor would I accept it in a patient with cytomegalic inclusion body disease; we see it too often quite normally. So I do not believe the x-ray examination is helpful, except to explain why they had trouble in putting a needle in the tibia.

Dr. John Craig.—This child at autopsy was still quite obviously premature; she measured only 47 cm. in length; the head size was normal, and there was no enlargement of the heart or the brain. There was fresh blood in the nares. The peritoneal cavity contained a small amount of icteric fluid and the liver was considerably enlarged, about 50 per cent over the normal. The lungs were quite firm throughout, especially in the lower lobes, and microscopic examination showed a diffuse chronic pneumonitis with much proliferation of the alveolar septal cells. There were few polymorphonuclear cells in this lung. Many areas of hemorrhage were noted which we believe were the cause of the apparent terminal hematemesis. There were large numbers of giant cell forms throughout the lung, a tremendous amount of septal cell proliferation. The infiltration of the lung was almost all mononuclear in character, and must have been present for a long time, I believe, before death occurred. It is surprising that no auscultatory findings were demonstrable. The spleen was about five times normal size. It was quite moist on cut surface and in the spleen itself there was a diffuse infiltration with both erythroid and myeloid forms, and large numbers of mononuclear cells. We were not able to demonstrate any of the inclusion cells in the spleen. There was little evidence of erythrophagocytosis or of

Fig. 1.

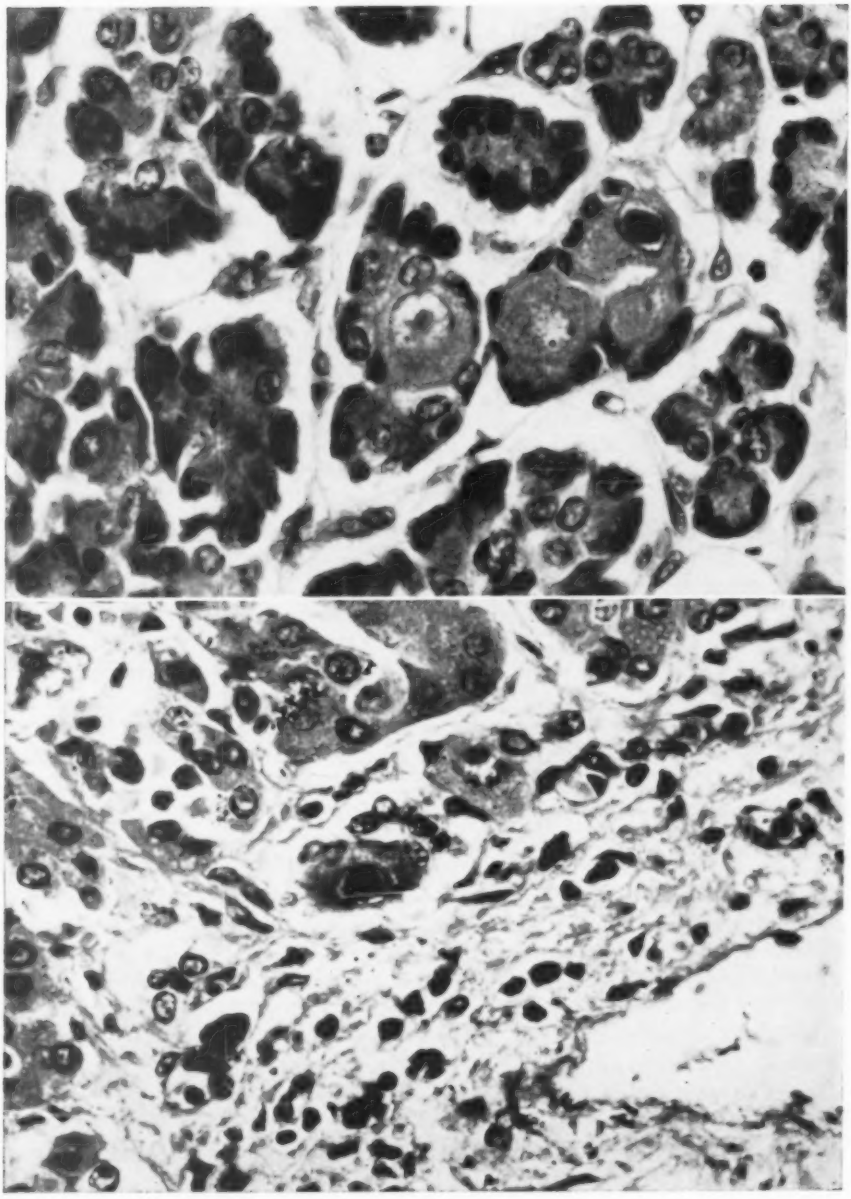

Fig. 2.

Fig. 1.—Pancreas. Intranuclear inclusion cells are seen in the acinar cells. (Hematoxylin and eosin; ×750.)

Fig. 2.—Liver. An intranuclear inclusion cell is present in the bile duct epithelium. There is a periportal and lobular inflammatory reaction. (Hematoxylin and eosin; ×700.)

Fig. 3.

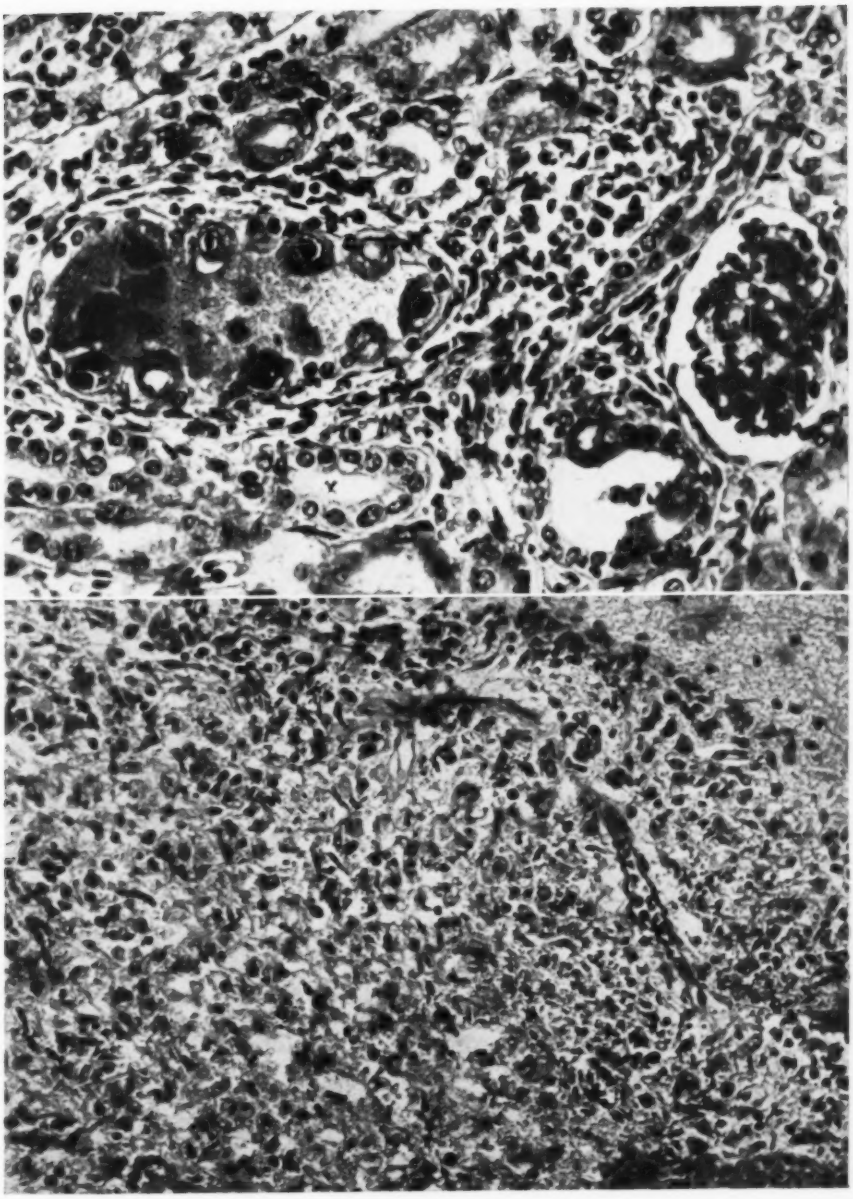

Fig. 4.

Fig. 3.—Kidney. Intranuclear and intracytoplasmic inclusion cells are present in the tubular epithelium. There is an interstitial nephritis. (Hematoxylin and eosin; ×350.)

Fig. 4.—Brain cortex. The edge of an area of necrosis; no inclusion cells are present. (Hematoxylin and eosin; ×190.)

thrombophagocytosis present. The pancreas showed well-defined areas of lesions consistent with disseminated cytomegalic inclusion disease (Fig. 1), and a considerable amount of inflammation with lymphocytes, and rarely erythropoietic elements. Scattered through the pancreatic acini and in the ducts were large cells, some of which contained inclusion cells. The liver showed a very diffuse hepatitis with large numbers of mononuclears, immature myeloid cell forms, not only throughout the pulp, but especially in the portal areas. There was a widespread bile stasis, with bile in many of the liver cells. There were inclusion cells in the bile ducts (Fig. 2). These have also been found rarely in other cases in the parenchymal cells, but is much more frequent to find them within the bile ducts themselves. We believe that the enlargement of the liver was primarily due to the tremendous amount of inflammatory reaction which was very diffuse throughout the liver parenchyma. This child still had large numbers of normoblasts, even a long time after birth, and yet still had a fairly high hemoglobin. In the kidney, the large cells with inclusions were mostly in the proximal convoluted tubules (Fig. 3), both intracytoplasmic and intranuclear. Some were also seen in the glomerular capsules. There was also diffuse inflammatory reaction in the interstitial cells of the kidney. It is apparent that the intracytoplasmic inclusions do not occur unless in the presence of the intranuclear inclusions, although one occasionally may see desquamated cells or completely degenerated cells in which the nucleus has disappeared, and then one may find some intracytoplasmic inclusions without accompanying intranuclear inclusions. The bone marrow was hyperplastic; we could find only

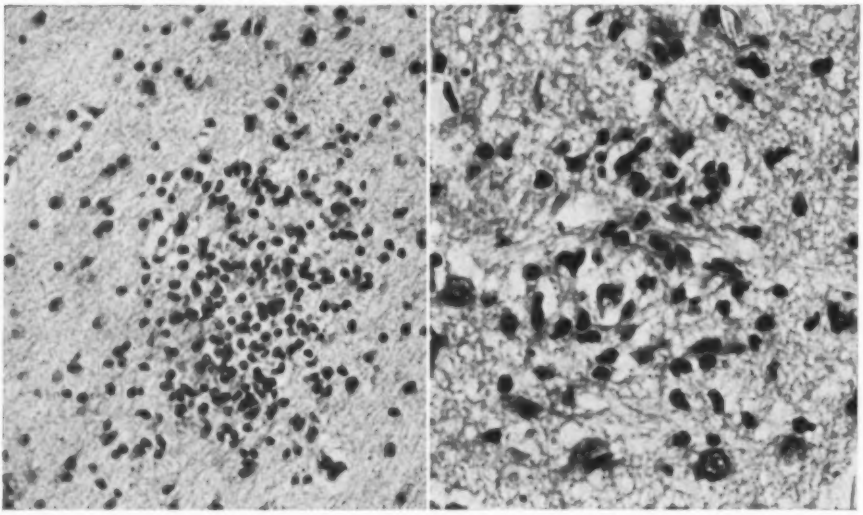

Fig. 5. Fig. 6.

Figs. 5. and 6.—Brain stain. Glial nodules present in the white and gray matter. (Hematoxylin and eosin; ×300 and ×450.)

rare megakaryocytes, and I believe that this child's purpura was probably due to failure in the megakaryocytic forms rather than in any antibody.

In the brain there was one small focus of hemorrhage in the occipital cortex, and no other gross lesions were noted. However, on microscopic examination there were numerous small glial nodules and areas of necrosis (Figs. 4, 5, and 6). Most of them seemed to be quite closely related to the ependyma and subependymal zones. In one of them I was able to find a single cell with an intranuclear inclusion. Dr. Farber and Dr. Wolbach[3] in 1932 examined the salivary glands in some 183 cases at autopsy and were able to demonstrate in about 12 per cent of them that these inclusions were present. One of the first men to emphasize that this could be a fatal infection was Wyatt in 1950.

It is worth pointing out that inclusion cells have been reported in almost any and every organ of the body, and almost in every tissue; in the earlier cases it was thought that they appeared only in epithelial organs, and especially in tissues lining ducts. Now it is recognized that they may occur in the heart, in the capillaries, in the skin, and in a great variety of tissues.

DR. FARBER.—The group in the two medical schools in St. Louis have been following this disease with great interest over the years, convinced that they would find a virus some day. When Dr. Rector came here from St. Louis some years after we had collected this large series with Dr. Wolbach, he called attention to the occurrence of these inclusions in the lacrimal gland, and so for a long time we took those out at post-mortem examination. Dr. Rector got his lead by taking them from wild rats in the city garbage heap in St. Louis—they have one there I am told—and he used to spend his evenings and week ends off lying in wait with a rifle, careful to shoot the rats anywhere except in the lacrimal gland. He collected a nice series, and proved that it occurred in rats as well as in guinea pigs. The clinical picture all through the years was disguised, if there was a clinical picture, by the occurrence of other diseases, such as miliary tuberculosis or congenital syphilis, or bacteriemia caused by one or another of the many organisms that cause death, and I think it is quite likely with the prevention of so much bacterial infection that this agent may become more important.

How to recognize it? I think Dr. Allen is to be congratulated on his logical differential diagnosis and the fine conclusion that he reached. The two generalized cases we had in the early 30's were labeled pathologically at that time hemorrhagic diathesis with inclusions in many organs and erythroblastosis. Of course we did not have the Rh factor to confuse us at that time, so that was a very simple diagnosis. I wonder if going back to these cases now, Dr. Craig, you would find that the picture is more clean-cut. I would continue to warn against the too rapid assumption that we have a very clean-cut disease entity recognizable without any question on clinical history or physical findings alone.

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Pediatric Profiles

Leonard Findlay

(1878-1947)

LEONARD Findlay's name will always be associated with Dr. John Thomson's as a pioneer of pediatries in Scotland. He was a most colorful character with a vivid personality and amazing energy. My association with him at the Royal Hospital for Sick Children, Glasgow, was for a relatively short period, from 1923 to 1930, when he left to live and work in London. His influence and thought still permeate the medical wards, and thirty years later I look back with pleasure on my association with him and find myself on ward rounds thinking of what he might have said or done when the tempo becomes dull or the students difficult to arouse to enthusiasm.

He was essentially an Edwardian—tall, spare, well dressed, and very distinguished. His hair was a coppery red, plentiful, and worn rather long; and in an age when most men were clean-shaven, he cultivated side whiskers. With a delightful disregard of prevailing fashion, he wore a starched white collar, such as used to be worn with evening dress at the turn of the century, and a dark tie which went twice around the collar, finishing in a bow in front. A monocle dangled casually from a black cord around his neck. He tried at times to do without the cord but this was never a success. In the more serious business of ward rounds or in reading he always wore horn-rimmed glasses. Although Edwardian in appearance, his general demeanor was Dickensian, with the manners and gestures of a member of the Pickwick Club. His colleagues, and indeed everyone who knew him at all well, would readily admit that he possessed a magnetic attraction, especially for the young doctor interested in research and academic medicine. Whatever you thought of his views and however much his illog-

icalities might arouse the worst in you, you could neither neglect nor forget him. His enthusiasm was infectious, and many a young doctor found himself working harder and longer than he had ever intended or thought possible.

Leonard Findlay was the son of a Glasgow doctor, Dr. William Findlay, whose family contributed one other doctor and an artist of some eminence. He was always a good student, qualifying with commendation in 1900 and obtaining his doctorate with honors in 1904. Pathology was his first love and he worked for several years in the laboratories of Sir Robert Muir. At this stage in the development of hospital medicine, in Scotland at any rate, physicians came to clinical medicine via pathology, and Findlay soon found himself Assistant to the Regius Professor of Medicine at the University of Glasgow.

About 1908 he became interested in rickets, and in the Department of Physiology carried out by himself and in conjunction with the late Professor D. Noël Paton many investigations into its cause. Vitamins were then unknown, or at least unnamed, and by confining dogs indoors while others were allowed out to run about he came to the conclusion that lack of exercise was one of the important factors in the development of rickets, failing to appreciate that the confined dogs were also deprived of sunshine and skyshine. For many years he pressed his views on the medical profession and stoutly denied the importance of sunshine and dietary factors. He would exclaim that "just because sunshine and cod-liver oil cured and prevented rickets, it does not follow that their lack is the cause of rickets. Cod-liver oil is not a normal constituent of a child's diet." In the end, however, he had to capitulate, and for some time before he left Glasgow in 1930 he had completely accepted the modern views.

It was his work on rickets from 1908 onward which must have made him turn to pediatrics which was then just being recognized as a special branch of medicine. In 1914 a new children's hospital had been built in Glasgow. It was ready for use but part of it was requisitioned for wounded soldiers until 1918. Findlay was given charge of the medical wards and appointed Lecturer in Diseases of Children in Glasgow University. In 1924, a chair of Medical Paediatrics was created and endowed by Professor Samson Gemmell, his old chief at the Western Infirmary.

Microbiochemical methods were then just being developed and Findlay was quick to realize the importance of these new methods in investigations in children, although he never performed any of the estimations himself. In his own work he had employed the old gravimetric method of estimating calcium as the oxide, using platinum crucibles in which to ash the blood. By working hard it was possible to do four or five estimations a week. Calcium balances were also carried out in the same laborious manner, but by careful planning of each experiment, a surprisingly large number of observations were made. Findlay soon acquired an international reputation and post-graduate students from many parts of the world came to study with him.

He was a restless man. Immediately after the First World War he spent a year as Director of Child Welfare to the League of Nations' Red Cross Society at Geneva. In 1930 he de-

cided at the late age of 52 to go south, which is the Scotsman's traditional road to fame and fortune. He was appointed physician to the Queen Elizabeth Hospital for Children in London and during the Second World War removed to Oxford, where he became physician to the Children's Department at the Radcliffe Infirmary.

Findlay had a penchant for upholding lost causes. Apart from his views on rickets he was inclined to support old-fashioned and at times unorthodox ideas. This was always a matter of surprise to those not closely associated with him. He was well versed in the literature of the time and knew of the more recent opinions, but it seemed that he could not readily accept anyone else's work; he must prove it for himself.

One always had to be careful in argument with him as he would marshall his facts to good advantage and woe betide the poor junior who made, perhaps unthinkingly, a loose statement. Quick as a flash, Findlay would say, "What right have you to say that?" and if the junior could not produce adequate evidence the discussion would end in his having to delve into old case sheets and the literature to prove or retract his statement. The daily ward rounds were never dull. Often only one or two patients were seen for heated arguments arose and the end of the allotted time would find the bed strewn with books and journals, the sister and nurses trembling, and perhaps tempers near breaking point. Then the air would clear and his essential kindness emerge. Still talking he would retire to his room for tea with myself in attendance. Sister would pour out his tea and in the manner of the common man and in defiance of convention he would pour it into his saucer, blow on it, drink it hastily—and back to work. He had much histrionic ability and never shunned the limelight. His fits of "temper" I suspect were merely his way, dramatic as it certainly was, of stimulating his students or driving home a point. Certainly no one bore him any ill will. On the contrary we rather looked forward to the storm and felt elated when we were able to ride it out and sail serenely into the calm waters which lay ahead.

His Sunday morning meetings were memorable. His staff would meet him in his room at 11 o'clock to discuss the deaths and dismissals of the week before. We sat on hard backless benches while he sat in an armchair behind a small desk. During the meeting he smoked Burmese cheroots at an incredible speed, blowing out enormous clouds of blue smoke. When the cheroot became too short for comfort he would casually put it in his pipe and carry on. (The story of his midnight request for another cigar when a guest of the late John Howland is too well known in America to be repeated here but it was a characteristic gesture which would have caused no surprise in Glasgow.) He had little sense of time and sometimes the meetings would not finish until 2 o'clock in the afternoon and many a good Sunday dinner was spoiled. The meeting could not finish until all the case sheets had been dealt with, and as each history had to be read through, there were no short cuts. This thoroughness which was so much a part of his make-up can be exemplified by the fact that for his small book, *The Rheumatic Infection in Childhood*, he succeeded in examining or learning the fate of 693

of the 701 patients with the infection who had passed through his wards during the preceding sixteen years.

Findlay had no hobbies. He was not interested in games, and although known to have played golf occasionally, he had a slight contempt, I suspect, for those who spent so much of their time in trying to acquire a little proficiency at the game. He was specially interested in the arts, and in particular, the theater, pictures, and old furniture. His real "hobby," however, was talking. He loved an argument and his greatest pleasure was to spend an evening with old friends in discussion of some philosophical subject far removed from medicine. I have the most pleasant and vivid recollections of motoring through to Edinburgh with him on Sunday afternoons to visit the late John Thomson. In the book-lined consulting room in Edinburgh the talk was not often of pediatrics but usually on general topics and reminiscences. It was indeed a great privilege to enjoy such company.

Many of us thought at the time that his move to London was a mistake. He was, I think, never happy there. Shortly after his retiral, he began to suffer from intermittent claudication but nothing daunted he took up gardening with his customary enthusiasm. In spite of several warnings he set about the task of altering the whole layout of his garden, even to the extent of building new stone dykes. His death occurred suddenly, as he would have wished, while actually engaged in this task, and so passed a lovable, enigmatic personality, whose dynamic influence still pervades the school of pediatrics which he founded.

Stanley Graham

Comments on Current Literature

PATTERNS OF INFECTION IN POLIOMYELITIS

THE development of convenient, objective and relatively inexpensive laboratory procedures for the study of virus infections has enabled workers in this field to obtain useful information concerning the natural history of virus disease. Of special interest to the practicing physician are recent epidemiologic studies of poliomyelitis which can provide him with information of value in attempting to give logical advice to patients and their families.

In the *New England Journal of Medicine* (Dec. 1, 1955) Nolan, Wilmer, and Melnick[1] report the investigation of an outbreak of poliomyelitis in a small community of high socioeconomic level. Studies carried out by means of tissue culture methods, complement fixation, and by neutralization procedures emphasized the highly invasive nature of the disease, and revealed that in this outbreak the stream of infection in the community was a narrow one. The initial focus of the epidemic was a small nursery school; the infection was carried from this point into the community by the nursery school children, mainly to their families, and to intimate contacts of their families. The outbreak comprised sixteen cases, of which six cases occurred in adults ranging in age from 27 to 35 years. It was of interest that every adult patient with clinical poliomyelitis was the parent of at least two small children. In this outbreak, the spread of poliomyelitis virus infection within the family group was illustrated by a well-documented study on one particular family consisting of seven members, the parents and five children. A 4-year-old boy in this family, who had attended the nursery school, developed typical symptoms of paralytic polio; his brothers, aged 7 and 3 years, experienced minor illnesses a few days later. The remaining four family members remained well from all indications. However, type I poliomyelitis virus was recovered from stool specimens of all the family members, except a girl of 10 years: from specimens of father, 37 years, mother, 35 years, sister, 8 years, two brothers, 7 and 3 years, who had minor illnesses, as well as from specimens of the 4-year-old boy, who was the one family member suffering from paralytic poliomyelitis. These virus isolation results were paralleled by comparative complement-fixing antibody studies carried out on all members of this family.

An evaluation of the over-all investigative results of this epidemic outbreak indicated that the virus of poliomyelitis was isolated readily from fecal material in 88 per cent of patients with clinical disease and from fecal specimens obtained from 54 per cent of the contacts. Various minor illnesses occurred in the community at the time of this outbreak; it was significant that all those whose symptoms were suggestive of poliomyelitis, but which were not definite, gave a history of exposure to a patient, or to an intimate contact of a patient with poliomyelitis. The complement fixation test proved to be a valuable aid in verifying infection with polio virus, the results being consistently in accord with those of the virus isolation procedures. Complement fixation tests

indicating recent infection with polio virus were positive in 92 per cent of patients, and in 40 per cent of their contacts.

Another well-documented epidemiologic report covering a "Winter Outbreak of Poliomyelitis in New York City" appears in the January, 1956, issue of the *American Journal of Hygiene*.[2] These authors, Melnick, McCarroll, and Horstmann, took advantage of an unusual opportunity to study an outbreak of poliomyelitis occurring in January, 1955, at a time when the weather had remained unusually cold, the temperature for weeks following the onset of the first case averaging 28.7° F., or 4.2° below normal for this area. Three cases of polio occurred in one wing of a building under conditions which prompted an epidemiologic investigation. The six-story structure consisting of two connecting wings is the property of The New York Hospital, and serves as a residence for married house-staff doctors and their families, as well as for unmarried personnel. The children attend a nursery school operated only for occupants of the building. The first of the three cases of poliomyelitis was that of a 3-year-old girl who became ill on Jan. 7, 1955. The child lived on the fourth floor of the south wing and attended the nursery school regularly. The second case, that of a 29-year-old father, occurred ten days later; this family, residing on the second floor of the south wing, had a 3-year-old son attending the nursery school. The third resident of the wing who developed poliomyelitis (ten days following onset in Case 2) was a 33-year-old mother who was in the sixth month of pregnancy at the time, and had received 20 ml. of gamma globulin six days prior to the onset of symptoms. Her son, 21 months of age, had not attended the nursery school, but had been in close contact with other children in the building who were nursery school members. Type I poliomyelitis virus was recovered from stool specimens of all three clinical cases, and the same type was isolated from fecal specimens obtained from five other members of their family.

An epidemiologic study among the apartment occupants was begun by the authors soon after the occurrence of the third case. Blood samples, rectal swabs, and stool specimens were obtained from various residents of the building. Complement fixation tests carried out immediately on the blood specimens indicated that many were strongly positive for type I polio virus. This information, available within twenty-four hours after the specimens were submitted to the laboratory, was verified by the isolation of type I virus from rectal swabs or from fecal specimens, suggesting that this type of polio virus was widespread in the apartment house. All three of the patients with clinical poliomyelitis were found to be shedding type I polio virus, as were five other members of their families. Of a total of 108 persons who submitted stool specimens for testing, twenty-three were found to be harboring type I virus, fifteen of these being children, eight being adults. No strains other than those belonging to type I were recovered. It appeared of particular significance that every adult excreting virus was the parent of at least one child also found to be excreting virus. Multiple infection in the family was the rule, and there was no instance of a single virus carrier in any family. In this study no adults in households without children were found to be harboring virus, emphasizing again the important role played by children, particularly young children, in the spread of this viral agent.

In order to obtain some idea of the distribution and the duration of polio virus in the apartment house, samples of sewage from both north and south wings of the building were collected at weekly intervals and cultured for the presence of virus. Sewage samples from both wings of the building yielded type I polio virus when first tested on February 2. The virus was present in sewage material from the south wing for three successive weeks,

indicating that the agent persisted in the sewage from that part of the building, where the three clinical cases occurred, and where the major number of contact infections was found. Simultaneous samples from the water supply failed to yield virus.

The pattern of household infection in this outbreak was of epidemic interest; the presence of susceptible children in the family appears to have been the single most important factor in determining spread of infection. The majority of infected adults was from families with children; a small number was composed of housewives with no children of their own but who had close association with young children; of forty-eight persons having no children of their own and no repeated contact, only four became infected. Once the virus was introduced into a family group, spread to all susceptible members of that household occurred, only two exceptions being noted: two fathers showed antibodies to type II polio virus, and none to type I.

As the authors point out, "these results emphasize the extremely high contagiousness of poliomyelitis virus when introduced into a group of susceptible individuals"[2]; the importance of close contact in the spread of this infectious agent was illustrated in their study by the high infection rates observed in adults and in children "in households where close and frequent physical contact with small children is common."[2] These authors emphasize likewise "the advantages of the complement fixation test for rapid easy confirmation of recent infection, clinical or inapparent,"[2] and its value in early recognition of epidemics and in tracing patterns of infection.

RUSSELL J. BLATTNER.

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Correspondence

To the Editor:

Almost simultaneously with our reading of Drs. Brainerd and Olmsted's article on intoxication of infants following the administration of Tyzine (JOURNAL OF PEDIATRICS, February, 1956), we encountered such a case in our clinic.

W. L., a 5-week-old white male, was brought to the Madigan Army Hospital Pediatric Outpatient Clinic on Feb. 21, 1956, in a stuporous condition. Mother related that at a routine post-partum check on herself she had requested "something for the baby's cold" from her obstetrician. Tyzine, *0.1%* was prescribed and she was instructed to instill 1 to 2 drops in each nostril. At the pharmacy she was supplied a nasal spray bottle in lieu of dropper container. At 6:00 P.M., Feb. 20, 1956, the mother gave the infant *a single dose* as the prescription suggested. The child then slept soundly. When the child did not awaken and could not be roused an ambulance was summoned which brought the infant to the hospital at 12:00 NOON February 21. Examination at that time was negative except for the somnolent state from which the infant could now be roused by stimulation to produce a sleepy cry. After a period of observation the infant was released to the parents.

The parents brought to the clinic the blue plastic spray bottle given them by the pharmacist. They insisted that they had not given the infant more than the prescribed dose, but it is likely that he did receive an overdose. The preparation was administered with the infant lying on his back and the tip of the dispenser inserted into the nostrils.

A single squeeze of the container in the inverted position will deliver a stream containing *0.3* to *0.5* c.c. of the solution, about 10 times the amount contained in a drop.

That the danger is not limited to infants is illustrated by the case of an intern at this hospital who administered Tyzine to himself for a cold. Being unfamiliar with the use of the spray container he tipped his head back and squeezed the inverted bottle. He immediately experienced discomfort in the nose and so blew it clear. For the next 15 to 20 minutes he was so dizzy he was unable to carry on and had to lie down.

An unsafe condition has been recognized and remedial action should be taken. The manufacturer should be induced to label the *spray* bottle to preclude its use on infants. Pharmacists should be alerted to the danger of furnishing spray containers when the prescription calls for drops.

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[Editor's Note: Several letters have been received referring to the CPC in the March issue of the JOURNAL, suggesting that the diagnosis of "milk allergy" should be considered. In a discussion of the hematological picture the point has been made that anemia of an iron-deficiency nature, or one with a megaloblastic tendency as in this case, has never been noted with milk allergy. We publish one of the letters to the Editor.]

To the Editor:

I feel compelled to add one major diagnostic possibility to the differential diagnoses in Dr. Apt's excellent discussion in the Children's Medical Center Clinical Pathological Conference published in THE JOURNAL OF PEDIATRICS, dated March, 1956. This omission probably will be noted by many of your readers just as it may have been considered and rejected during the patient's hospitalization without entering the protocol.

The nasal symptoms (usually attributed to an upper respiratory infection) at 5 weeks of age; the subsequent diarrhea and vomiting relieved temporarily by a change in the form of cow's milk protein and substitution of oral electrolyte solution; the resumption of diarrhea with skim milk feedings—all have been noted in milk sensitivity.[1] Blood in the stool has been reported as caused by milk allergy[2] and, in one local instance, severe to the point of near-exsanguination. The persistent diarrhea and smoldering upper respiratory infec-

tion in the twin sibling suggest a less severe milk sensitivity and strengthen this possibility in the infant discussed.

Milk allergy has been estimated to occur in 1 out of 15 infants[1] and any infant with persistent "cold," diarrhea, colic, or vomiting —singly or together—deserves consideration along this line. A simple confirmatory office test is the staining of stool mucus (easily obtained by rectal examination) for eosinophils. A therapeutic trial of soybean formula is likewise simple and ofttimes miraculous in effect.

WILLIAM F. MOORE, JR., M.D.

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News and Notes

Dr. John E. Gonce, Jr., Professor of Pediatrics and Chairman of the Department at the University of Wisconsin Medical School since 1924, died of coronary thrombosis on March 25. He was 62 years of age.

On April 4 a dinner was held in New York honoring Dr. Philip M. Stimson for "four decades of unceasing labor to help children conquer the afflictions of poliomyelitis and other diseases." A silver tray "in recognition of his service to children" was presented to Dr. Stimson by his associates at New York Hospital-Cornell Medical Center, where he is consultant in pediatrics and professor of clinical pediatrics, and the Willard Parker Hospital, where he was a staff member for over thirty-five years. Dr. Stimson, organizer and director of the poliomyelitis division of Knickerbocker Hospital in New York from 1945 to 1949, also received a distinguished service award from Dr. Hart E. Van Riper, medical director of the National Foundation for Infantile Paralysis.

The **American Board of Pediatrics**, through its **Subspecialty Board of Allergy**, and the Council on Medical Education and Hospitals of the American Medical Association, are developing a program for the approval of residency programs in preparation for certification in that subspecialty. Applications for approval should be submitted to the Executive Secretary of the American Board of Pediatrics, Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

A comprehensive review of recent progress in pediatrics designed for general practitioners as well as specialists will be presented at the **Eighth Annual Summer Clinics** of the **Children's Hospital in Denver** on June 27, 28, and 29. Guest speakers this year will be Dr. Harry Bakwin, Professor of Clinical Pediatrics, New York University, Dr. Thomas C. Moore, Associate in Surgery at the Indiana University Medical Center, Indianapolis, and Dr. Joseph C. Risser, Associate Professor of Orthopedics, College of Medical Evangelists, Los Angeles, Calif. Further information can be secured by writing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18, Colo.

A **Postgraduate Medical Seminar Cruise** sponsored by Duke University School of Medicine will sail from New York Oct. 27, 1956, by the S.S. "Nassau," 24,000 tons, completely air-conditioned, visiting Madeira, Casablanca, Cadiz, Palermo, Naples, and Rome (18 days New York to New York). Faculty: Dr. Wilburt Cornell Davison, James B. Duke, Professor of Pediatrics and Dean of the School of Medicine; Dr. William McNeal Nicholson, Professor of Medicine and Director of Post-Graduate Education; Dr. Lenox D. Baker, Professor of Orthopaedic Surgery; Dr. Leslie B. Hohman, Professor of Psychiatry; Dr. Edward S. Orgain, Professor of Medicine. For literature address Allen Travel Service, Inc., 550 Fifth Ave., New York 36, N. Y.

Books

Les Gamma-globulines et la medecine des enfants. Centre international de l'enfance, Paris, 1955, Masson et Cie, 289 pages. Price fr. 2,000 (French).

An interesting report edited by Dr. Raymond Gautier of a two-day seminar held in Paris in December, 1954, and organized by the Centre under the presidency of Prof. A. Tiselius of Uppsala. The seminar was divided into three main topics for discussion: I. Theoretical and practical problems. These included the physical-chemical characters of gamma globulin, methods of preparation, and immunological studies. II. The physiology and pathology of gamma globulin. The discussion in this section includes the origin and metabolism, clinical application and dosage, and the conditions of hyper- and hypogammaglobulinemia. III. In the third section its clinical use and value in specific diseases including, among others, poliomyelitis, whooping cough, hepatitis, measles, and chicken pox is presented. Some 40 pediatricians and biochemists from eleven different countries took part in the discussion and as a result the report brings together our basic and clinical knowledge of gamma globulin up until a year ago. It is well printed and illustrated and our only regret is the lack of an index.

Medical Photography, ed. 5. T. A. Longmore, London, 1954, The Focal Press, 990 pages. Price $15.00.

A technical manual on medical photography of interest to anyone who takes pictures of medical lesions and specimens. The text could be used with profit by many physicians who include photographs to illustrate articles submitted to medical journals for publication. The fact that it has gone through five editions since first published in 1944, and has more than been doubled in size, testifies of its usefulness.

Doctor and Patient and the Law, ed. 3. Louis J. Regan, M.D., LL.B., St. Louis, 1956, The C. V. Mosby Co., 716 pages. Price $12.50.

The frequency with which suits for malpractice have been brought against physicians, nurses, and hospitals in recent years makes a knowledge of legal medicine of increasing importance. This standard text by a physician and lawyer, who holds the Chair of Legal Medicine in two of the medical schools in Los Angeles, has been considerably revised and rewritten to bring it abreast of the more recent developments, as the Grievance Committees established by the medical societies. Throughout, the physician-patient relationship is emphasized.

Pediatric X-ray Diagnosis, ed. 3. John Caffey, M.D., Chicago, 1956, Year Book Publishing Co., 1059 pages.

Dr. Caffey's well-known text has become a standard work of reference. The new edition has been so extensively revised and enlarged as to make it a new text from a practical standpoint. Some 250 new illustrations have been added to keep the text abreast of the many advances which have taken place in pediatric roentgenology since the second edition in 1950. A number of these have to do with the recent development of cardiology. A new section on congenital dysplasia and congenital dislocation of the hip has been added.

Pathologic Physiology, ed 2. William A. Sodeman, M.D., Philadelphia, 1956, W. B. Saunders Co., 963 pages.

A revised edition of the one published in 1930. Chapters on Genetics of Abnormal Growth and Neoplasia by Macklin and the Nervous System by De Jong have been added. A number of the other chapters have been revised to keep pace with recent advances.

The Treatment of Eczema in Infants and Children. Lewis Webb Hill, M.D., St. Louis, 1956, The C. V. Mosby Co., 79 pages.

The series of papers on infantile eczema which appeared in the JOURNAL last year has been published in book form.

Editor's Column

THE "FUND-FOR-A-DISEASE" PROBLEM

THE national voluntary health organizations, which have increased in number to around twenty in recent years, are becoming a matter of concern. Problems are developing which involve not only the medical aspects, but even more the civic and community leaders who bear the burden and responsibility for raising the increasingly huge sums of money each year to meet the needs of the local hospitals, relief agencies, and service organizations. Most of these national health societies have their origin in a group of physicians with a special interest in a particular disease, who quite altruistically feel that if lay interest can be aroused, funds can be secured for educational and research purposes. However, decided differences exist in the objectives of the various national organizations, in their control, and in the use of the funds raised.

A critical interest in the "Funds" has been aroused in the last few years by the growth of community joint fund-raising plans, as a "United Fund," whose purpose is a most desirable and needed attempt to cut down the number of individual campaigns and solicitations for donations, and to reduce the tremendous aggregate cost and work of raising money. Important questions are being raised. One is the relative importance of the particular disease in the total health picture. A second question is how wisely the money raised is used. Closely connected with this is the cost of raising the fund and administering it, or expressing the question in another way, how much of the money raised is actually spent on the disease for which it was given.

It is not a new problem. A former president of the Rockefeller Foundation once stated that to exalt one disease "to get it out of focus and to urge it at the expense of other essential factors is unscientific, wasteful, and misleading."* In a study of voluntary health agencies made for the National Health Council in 1946 the soundness of sentimental appeals for particular conditions was challenged. Referring to polio the question was raised as to whether the extent of the disease warranted so extensive an organization in 2,600 counties and so intensive an appeal to practically every adult in the country.

A few of the Fund-for-a-Disease groups have joined in the trend to participate in local joint fund-raising efforts, as the Cerebral Palsy Association, while other national organizations, notably the Polio Foundation and the Heart and Cancer societies, have refused to allow their local chapters or organizations to participate in joint appeals for support. Some, as the Diabetes group, are still on the fence. As a result, public philantro-

*Quoted from the *Survey of Medical Research* published by the American Foundation.

phy has been described as a battleground in which the national health organizations are competing with local united campaigns for the health dollar. It is no wonder that many donors are becoming confused and disturbed by the situation. Little consideration has been given by the national organizations to local needs, or to the relative importance of the particular disease from a health standpoint, in beating the publicity drums for their own purposes. One wonders at times if part of this attitude may not be due to the influence in the national organizations of the large number of salaried nonmedical personnel engaged in fund-raising and administrative capacities in the particular organization. While the dislike to lose a job is understandable, nevertheless the great cost of raising the individual funds means that less of the dollar goes to the purposes for which it was solicited than the donor realizes.

One of the basic questions is the relative importance of the particular disease, a point that is seemingly totally disregarded in the efforts of these rival organizations in fund-raising. The following figures give two estimates of the relative importance of some of the "Fund" diseases, based on the number of victims involved. While there are differences in the two estimates both accentuate the same point.

	A*
Poliomyelitis	1.0
Muscular dystrophy	2.0
Multiple sclerosis	2.5
Tuberculosis	4.0
Cerebral palsy	6.0
Cancer	7.0
Mental disease	25.0
Arthritis and rheumatism	75.0
Heart disease	160.0

*Taken from an Editorial in the *New England Medical Journal* 252: 783, 1955.

	B*
Poliomyelitis	1.0
Muscular dystrophy	2.0
Cerebral palsy	5.5
Cancer	7.5
Tuberculosis	12.0
Mental disease	100.0
Heart disease	100.0
Arthritis and rheumatism	111.0

In this connection the amounts raised* by some of the "Funds" in 1954 is most enlightening, as they show a total lack of relationship between the relative importance of the disease based on the number of victims, and the amounts raised. What it really points out is the relative effectiveness of the publicity departments of the organizations.

	MILLION
National Foundation for Infantile Paralysis	$66.9
National Tuberculosis Association	24.7
American Cancer Society	21.3
American Heart Association	11.3
United Cerebral Palsy Association	8.3
Muscular Dystrophy Association	3.9
Arthritis and Rheumatism Foundation	1.8
National Association for Mental Health	1.5

Accepting the estimates in Column B above as to incidence, $66.90 was raised for each victim of polio in 1954, compared with $1.13 for each victim of heart disease and 0.163 cents for each victim of arthritis and rheumatism.

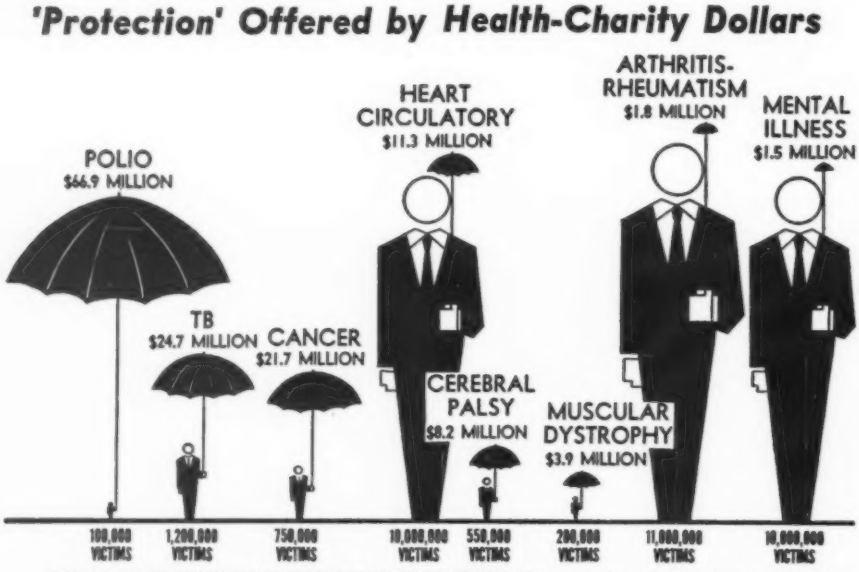
It is a lopsided, fantastic situation and points out what happens when a particular disease is "exalted."

It is far from our thought that the voluntary health organizations are without merit. Some have rendered a distinct service by aiding the development of local facilities for the care of the disease in which they are interested. Some have stimulated and used a considerable percentage of

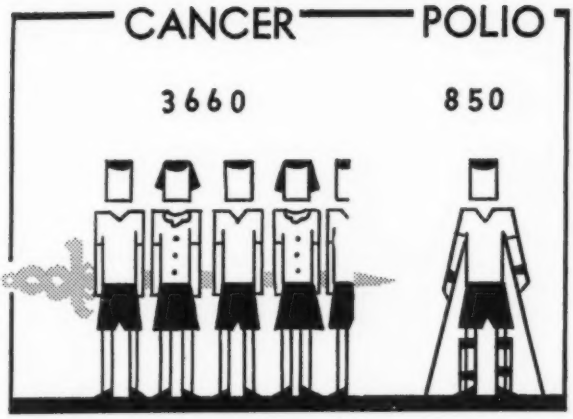
*Taken from a series of articles in the *St. Louis Globe-Democrat*, February, 1956.

their funds for research. Beyond question they have been an important factor in stimulating the interest that lies back of the increasing Federal appropriations for medical research, and the development of the National Health Institutes for the technical use of the Federal funds. Nor is it our feeling that they have served their usefulness and the time has come when they should be discontinued. But certain facts stand out. One is that by publicity methods some have raised funds far above the importance of the particular disease in relation to the total health needs. A second is the somewhat arrogant noncooperative attitude of some which refuse to recognize local needs and conditions in the communities in which they seek to raise funds—somewhat a selfish "to hell with all else" attitude. A third fact is that the excessive cost of independent fund-raising campaigns means that a considerable part of the money the donor thinks he is giving to aid in the amelioration of a specific disease is lost in paying for nonmedical activities. For example, a recent report[1] stated that eight of the major national health agencies in 1954 spent $11,500,783 in fund raising, while only $12,892,616 of the total amount raised was allotted for medical research.

Recently (February, 1956) the *St. Louis Globe-Democrat* published a series of eight articles which reflected a careful study of the work of eight of the Fund-for-a-Disease organizations. They were illustrated with striking graphs and charts which tell the story most dramatically. We are indebted to the *Globe-Democrat* for permission to reproduce some of the charts which will be of interest to our readers.

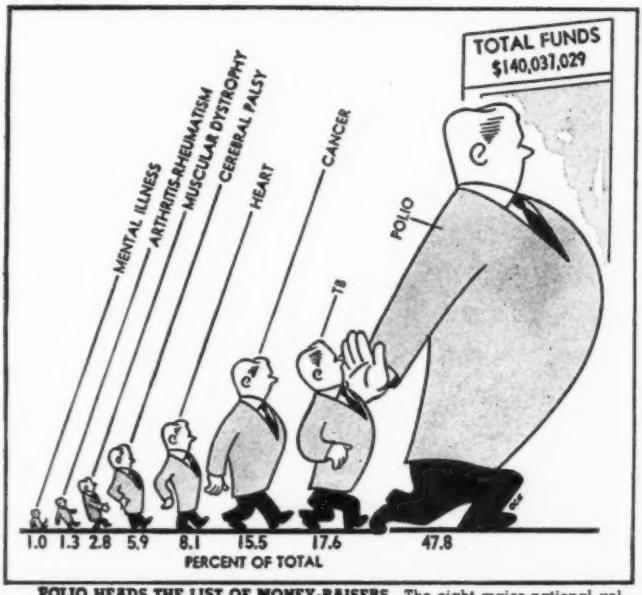


THESE ARE THE AMOUNTS OF MONEY RAISED NATIONALLY by our major voluntary health agencies—compared with the number of persons afflicted by the diseases those agencies fight. Amounts given are for 1954, latest year for which national fund-drive figures of all eight agencies are complete. The number of polio victims includes carry-overs. Only 38,741 polio cases occurred that year—and it was an epidemic year.

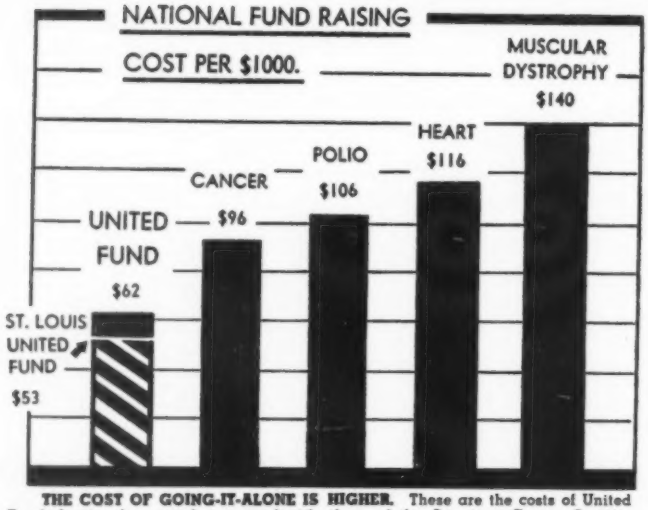


Cancer Kills More Than 4 Times As Many Children as Polio

THESE ARE THE FIGURES (from the National Office of Vital Statistics) on cancer and polio death tolls for children under 15 years of age in 1954—latest year available. Cancer killed 3660 children, polio only 850. (Sword is the symbol of the American Cancer Society's Cancer Crusade.)



POLIO HEADS THE LIST OF MONEY-RAISERS. The eight major national voluntary health agencies raised a total of $140,037,029 in 1954 (latest year in which figures for all national drives are complete). The National Foundation for Infantile Paralysis got nearly half—47.8 per cent — of that total. Amounts the other agencies got are shown in percentages of the total.



THE COST OF GOING-IT-ALONE IS HIGHER. These are the costs of United Funds (national average), compared with those of the American Cancer Society, the National Foundation for Infantile Paralysis, the American Heart Association and the Muscular Dystrophy Associations of America. St. Louis' United Fund costs are cheaper—only $53 per $1000 raised—than United Funds' national average.

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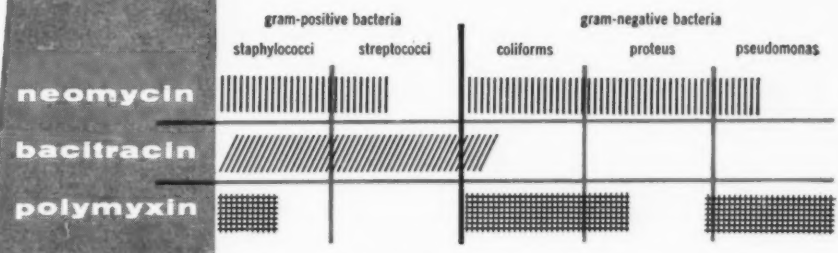

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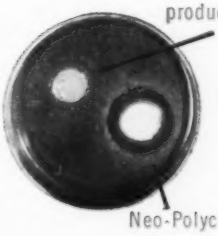

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1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. Med. 53:2233, 1953. 2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951. 3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949. 4. Sobel, A. E.: Scientific Exhibit, A.M.A. Meet. 1955. 5. Marks, M. M.: Missouri Med. 52:187, 1955.

New... *and a Major Advance in Treatment of* ASTHMA

MEDIHALER™

Fully effective nebulization with your favorite bronchodilator*

A nonbreakable plastic case, convenient for mother to carry in pocket, purse, or picnic basket, contains Medihaler Oral Adapter and medication* (in leakproof, spillproof vial).

Insert valve of medication vial snugly into Adapter... Takes only a moment... Nothing to pour... No complicated gadgets to assemble.

•

Simple and notably safe to administer to children... Uniform dose every time... True nebulization... No choking liquid to run down pharynx.

UNIFORM DOSAGE

SELF POWERED

ECONOMICAL

a) Unbreakable Adapter

b) No Medication Loss from Spillage or Oxidation

UNIFORM PARTICLE SIZE

80% between ½ and 4 microns radius

***MEDIHALER-EPI™**

0.5% solution of epinephrine HCl U.S.P.

***MEDIHALER-ISO™**

0.25% solution of isoproterenol HCl U.S.P.

Only one or occasionally two applications abort most attacks. Each 10 cc. vial of Medihaler medications provides 200 inhalations. Most economical... No waste... Foolproof.

ANOTHER RIKER FIRST

follow this simple form of ℞

Riker
LOS ANGELES

℞ Medihaler-Iso
and
Medihaler Oral
Adapter

for diarrhea..

LACTINEX®

Granules & Tablets

LACTINEX GRANULES and LACTINEX TABLETS contain a standardized viable mixed culture of Lactobacilli acidophilus and bulgaricus with the naturally-occurring metabolic enzymes produced by these organisms.

LACTINEX TABLETS—A clinically proven treatment for gastrointestinal disturbances, including diarrhea[1,2] (antibiotic induced and others) in infants and adults.

LACTINEX GRANULES—An especially designed dosage form (served on cereal, food or with milk) of this effective product for the pediatric and geriatric patient.

Dosage: Three or four tablets or one packet, three or four times a day.

Supplied—tablets in bottles of fifty—granules in boxes of twelve, one gram packets.

1. *Siver, Robert H.: Current Medical Digest, Vol. XXI, No. 9, September 1954.*
2. *McGivney, John: Texas State Journal of Medicine, Vol. 51, No. 1, January 1955.*

HWD

HYNSON, WESTCOTT & DUNNING, INC., Baltimore 1, Md.

Somnos®

CAPSULES AND ELIXIR CHLORAL HYDRATE

smooth sedation for the hypersensitive child

MAJOR ADVANTAGES: Induces "natural sleep and sedation without any medullary depression."[1] "One of the safest of all sedatives."[2] Affects no vital function.

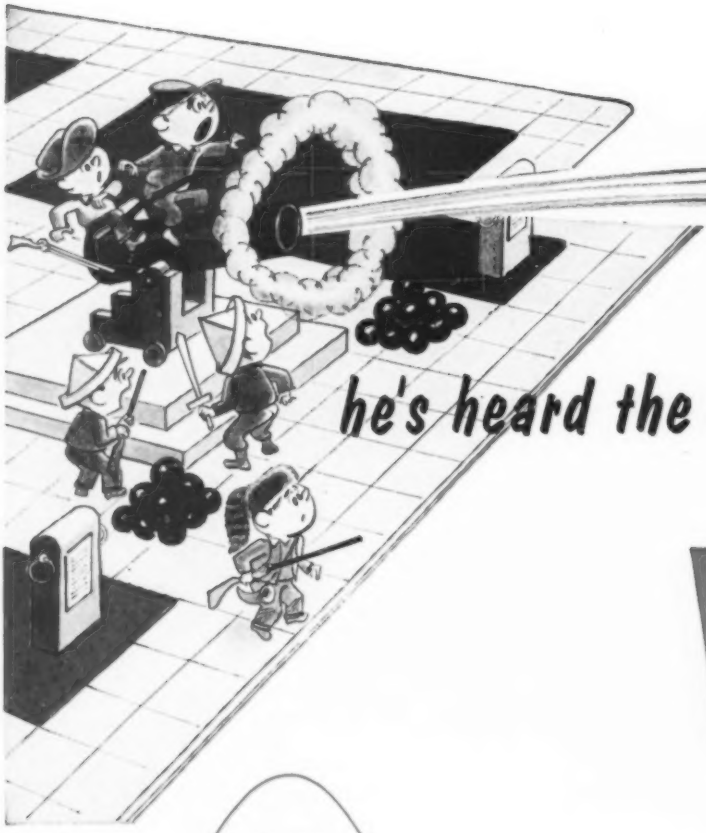
Whenever restlessness makes sleep difficult, prescribe SOMNOS *Elixir* for your young patients. In full dosage it acts within an hour; sleep is quiet; the patient awakes refreshed, without after-effects. In smaller amounts SOMNOS provides useful sedation when nervousness is a problem.

SOMNOS *Elixir* (1.6 Gm. per fl. oz.) is palatable, easy to give in milk, ginger ale, or other liquids. Dosage is readily adjusted. For older patients, SOMNOS is available as *Capsules* (0.25 and 0.5 Gm).

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

References: 1. West Virginia M. J. 49:292, 1953. 2. Mod. Med. 19:59, 1951.



he's heard the call for

VI-D

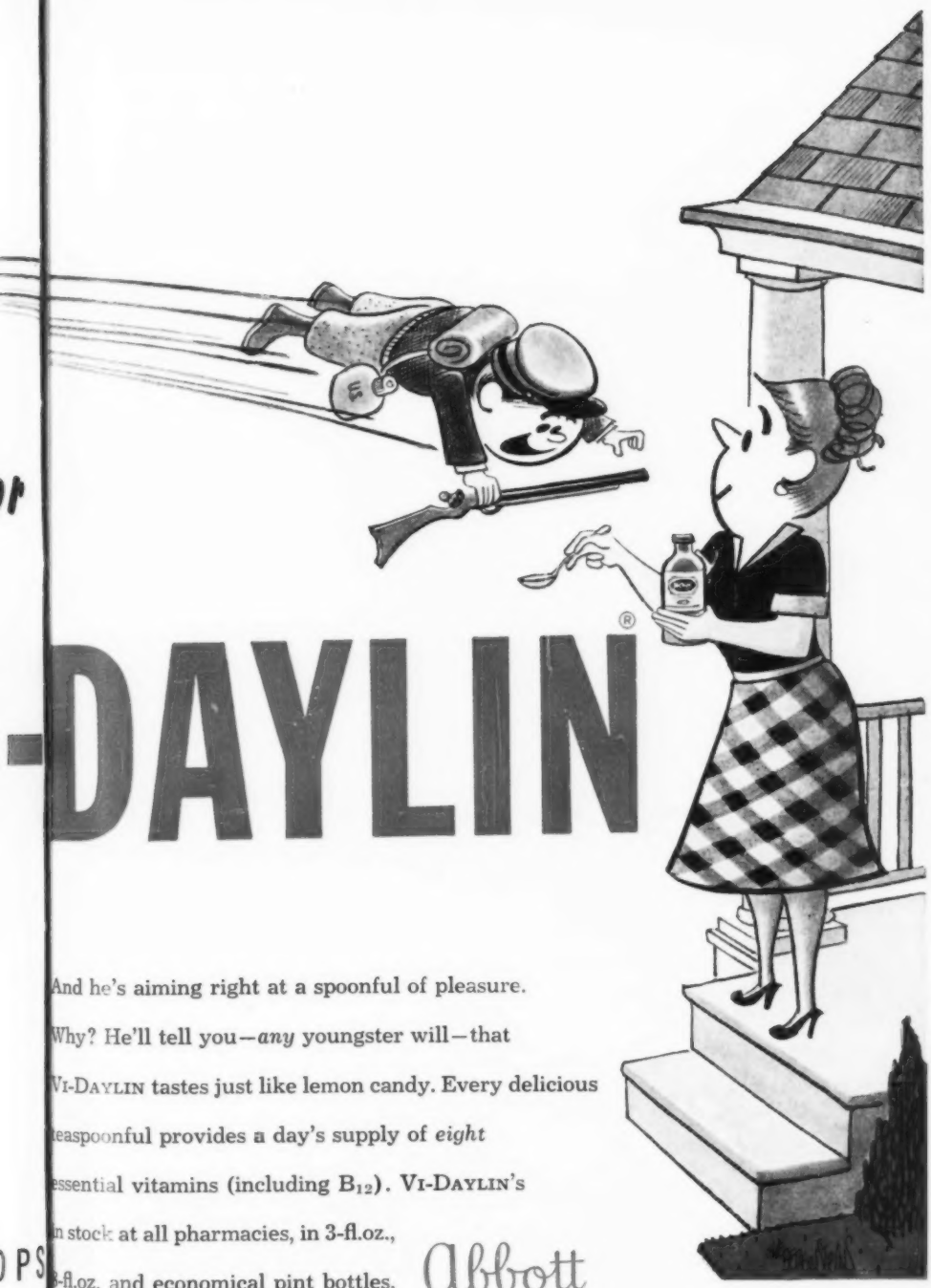
Each 5-cc. teaspoonful of VI-DAYLIN contains:

Vitamin A	3000 U.S.P. units (0.9 mg.)
Vitamin D	800 U.S.P. units (20 mcg.)
Thiamine Hydrochloride	1.5 mg.
Riboflavin	1.2 mg.
Pyridoxine Hydrochloride	1.0 mg.
Ascorbic Acid	40 mg.
Vitamin B_{12}	3 mcg.
Nicotinamide	10 mg.

...and for infants,

VI-DAYLIN® DROPS

604163



-DAYLIN®

And he's aiming right at a spoonful of pleasure.

Why? He'll tell you—*any* youngster will—that

VI-DAYLIN tastes just like lemon candy. Every delicious

teaspoonful provides a day's supply of *eight*

essential vitamins (including B_{12}). VI-DAYLIN's

in stock at all pharmacies, in 3-fl.oz.,

-fl.oz. and economical pint bottles.

Abbott

Report | from Carnation Research Laboratory

Scientific Staff Conferences

Regular conferences of the entire research staff are held so that the pooled knowledge of these highly qualified men may establish broad general directions for major research projects. Such conferences also keep the entire staff informed of current progress in all six major research divisions.

Continuous, Planned Research

protects the uniform optimum high quality of both established and new Carnation food products.

6 Research Divisions

Carnation general research projects are conducted under six major laboratory divisions: three Dairy Product Laboratories, the Nutrition Laboratory (chemical and biochemical research), the Cereal Laboratory and the Analytical Laboratory.

CARNATION PROTECTS YOUR RECOMMENDATION WITH CONTINUOUS 5-PHASE RESEARCH:

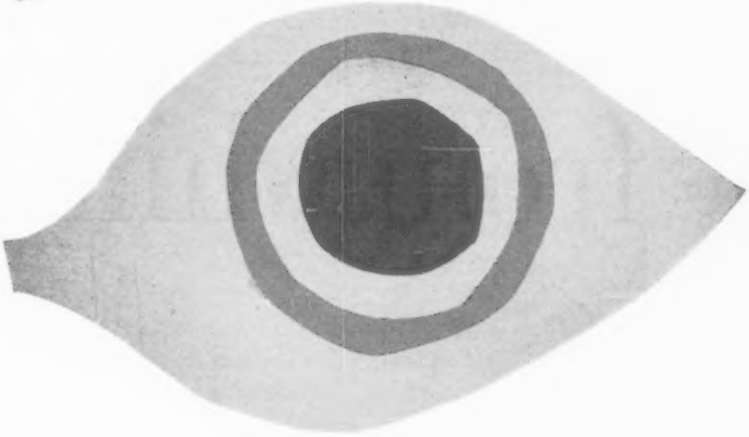
Carnation Research Laboratory,
Carnation Farms,
Carnation Plant Laboratories,
Carnation Central Product Control Laboratory,
Carnation-sponsored University and Association Research.

"from Contented Cows"

shampoo without tears

PROOF

Johnson's Baby Shampoo produces no irritation when introduced into conjunctival sac of rabbits.



- does not burn or sting the eyes
- nonirritating, hypoallergenic
- cleanses thoroughly and rinses completely

bettering baby care through specialized research

BABY PRODUCTS DIVISION

Johnson & Johnson

NEW

from whining to

NEW

BONADOXIN® DROPS

stop infantile colic...

in hours

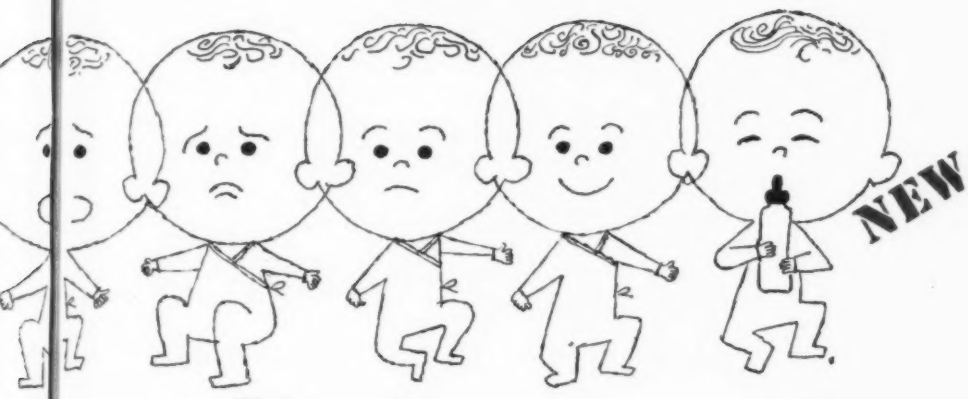
without barbiturates

without belladonna

ROERIG Rx

Chicago 11, Illinois

1. Dougan, H. T.: Bonadoxin Drops: an effective oral therapy for infant colic & pylorospasm. Journal-Lancet (May) 1956. In press



g to dining

BONADOXIN DROPS attack the known mechanisms of infantile colic with

Antihistamine action: to relieve colic of possible allergic origin.

Anticholinergic activity: to break the cycle of emotional tension, smooth muscle spasm, pain.

Tranquilizing effect: to calm the infant and permit sleep.

B_6 prophylaxis: added protection against colic and infantile convulsive disorders due to pyridoxine deficiency.

NEW

Clinical studies. Bonadoxin Drops were effective in the therapy of infant colic and pylorospasm in 22 (88%) of 25 patients. Dramatic improvement was observed in some of them. There were no side effects, and complete tolerance and acceptance were observed in all infants. The authors were able to regulate dosages with great flexibility, adjusting them upward, in several instances, for better management of intestinal complaints. All children found the lime-flavored liquid agreeable. [1]

Each cc. BONADOXIN DROPS contains:

Meclizine Dihydrochloride	8.33 mg.
Pyridoxine Hydrochloride	16.67 mg.

Dosage:	**Age**	**cc.**	**Drops**
	Birth-3 mos.	0.5 to 1.5 cc.	15-45 daily
	6 mos. to 2 yrs.	1.5 to 3.00 cc.	daily
	2-6 yrs.	2.00-4.00 cc.	daily
	older children	3.00-6.00 cc.	daily

Supplied in 30 cc. dropper bottles.

Standards in Pediatrics

DIAPARENE BABY POWDER

DIAPARENE RINSE TABLETS

DIAPARENE BABY LOTION

DIAPARENE PERI-ANAL CREME

DIAPARENE OINTMENT

SAMPLES
AND
LITERATURE
ON REQUEST

Diaparene

HOMEMAKERS PRODUCTS CORPORATION, 380 SECOND AVENUE, NEW YORK 10, N. Y.

for otitis

'AEROSPORIN'® SULFATE

POLYMYXIN B SULFATE WITH PROPYLENE GLYCOL

OTIC SOLUTION STERILE

Specifically aimed at aural pathogens—

bactericidal to most gram-positive and gram-negative organisms, particularly *Ps. aeruginosa*, the commonest cause of otitis externa.

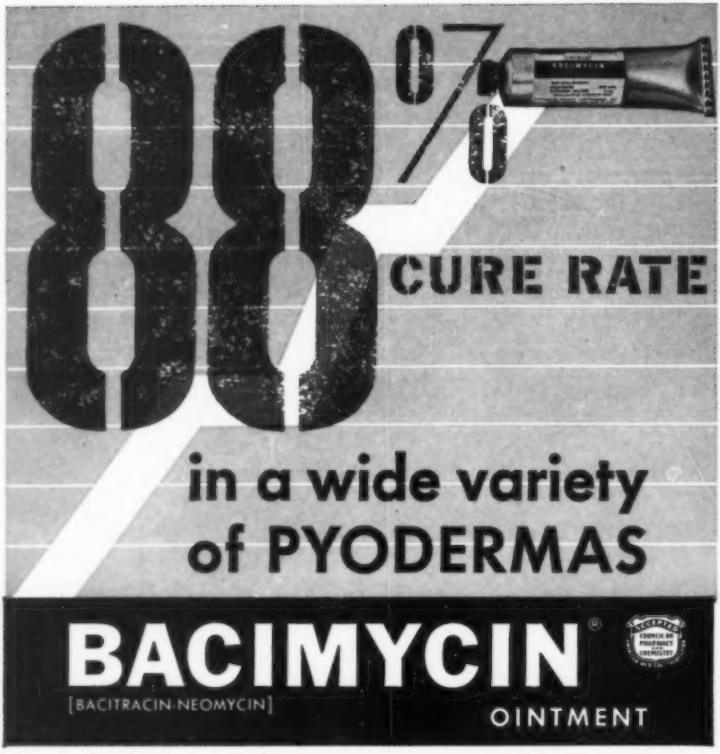
fungicidal to most of the dermatomyces found in the ear.

For otitis externa, whether acute or chronic, an exceptionally high percentage of complete clearance in a short time.

For chronic otitis media (when the ear drum is perforated); preferably in conjunction with systemic therapy.

Bottles of 10 cc. (with dropper)

Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe 7, New York



a first choice for dual antibiotic therapy

In a recent study[1] of 53 patients with various types of pyodermas, the use of BACIMYCIN Ointment "...resulted in a cure rate of 88%..." and not a single case of sensitization or primary irritation occurred.

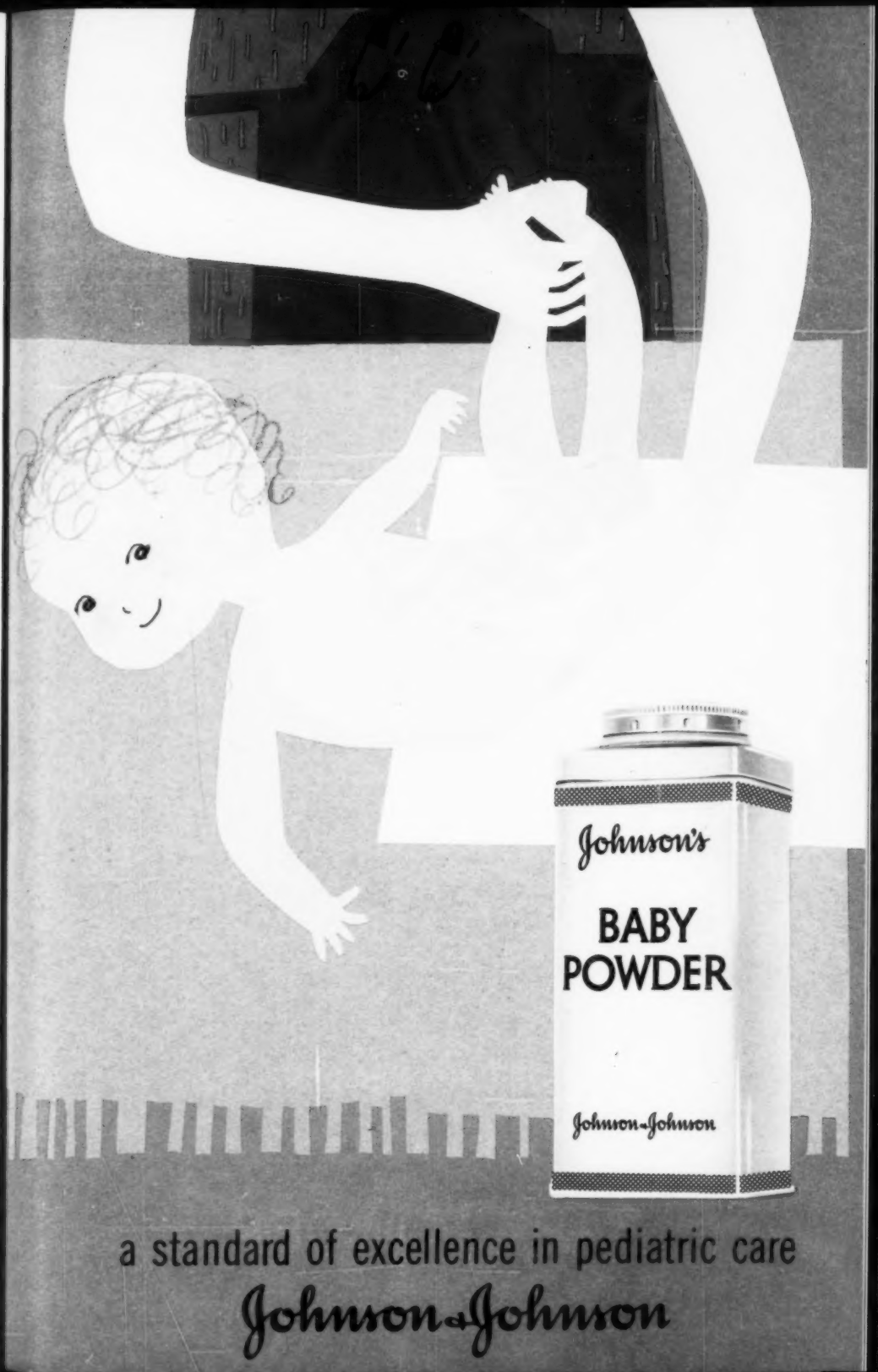
Impetigo, infectious eczematoid dermatitis, atopic eczema, secondary infections superimposed on dermatitis venenata, and folliculitis were among the common skin infections that showed marked improvement with BACIMYCIN therapy.

Supplied in ½-oz. tubes for prescriptions; in 100 gm. jars for hospital use.

Literature and samples on request.

1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366, Mar., 1954.

Walker LABORATORIES, INC. MOUNT VERNON, NEW YORK

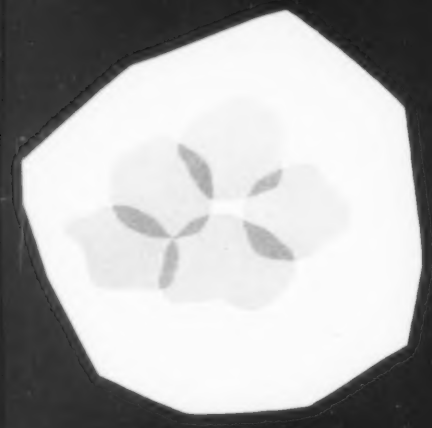


a standard of excellence in pediatric care

Johnson & Johnson

PROOF

excellent lubricant action



Smooth, flat platelets unique in the specially selected talc used in Johnson's Baby Powder. Note absence of any abrasive, irritating particles.

due to uniform, flat platelets

Johnson's

BABY POWDER

Johnson's Baby Powder contains the world's most suitable talc

Only Johnson's Baby Powder uses the whitest, purest Italian talc exclusively. This is specially processed and screened, then enhanced by clinically proved ingredients, to give a baby powder of unsurpassed quality.

excellent dry lubrication The specially selected talc in Johnson's Baby Powder insures uniformly smooth, flat platelets. These talc platelets glide smoothly—give the powder its unexcelled lubricant action and silky-soft feel.

exclusive buffering action Only Johnson's Baby Powder contains a special agent which neutralizes excessive acidity and alkalinity of the skin—helps prevent and relieve diaper rash, urine scald and chafing.

notably free from dust-cloud effect Special processing discards particles likely to be air-borne and inhaled.

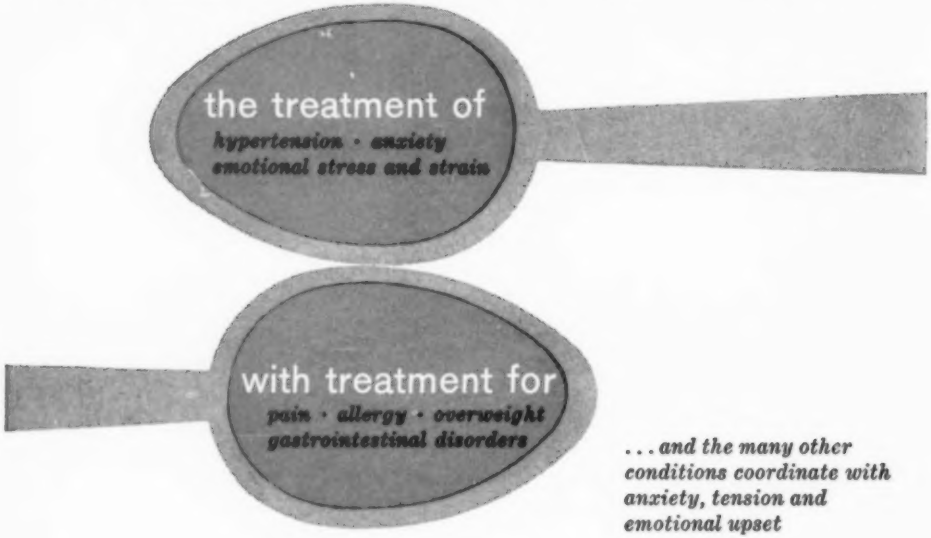
absorption without occlusion Johnson's Baby Powder contains no oil, does not occlude skin, and does not repel water. It blots up moisture for rapid evaporation—helps combat chafing and miliaria.

bettering baby care through specialized research

BABY PRODUCTS DIVISION

Johnson & Johnson

when you must combine...



. . . and the many other conditions coordinate with anxiety, tension and emotional upset

prescribe compatible

pleasant-tasting
highly compatible liquid
compounded with . . .
other agents
of your choice

The antihypertensive and tranquilizing effects of Serpasil can now be easily combined with other agents that you may wish to prescribe simultaneously. Serpasil Elixir is compatible with many other medications, such as Pyribenzamine® citrate (tripelennamine citrate CIBA) Elixir, dextro-amphetamine sulfate elixir, codeine phosphate, ephedrine sulfate, and sodium salicylate.

Each 4-ml. teaspoonful of light green, lemon-lime flavored Serpasil Elixir contains 0.2 mg. of Serpasil.

C I B A
Summit, N. J.

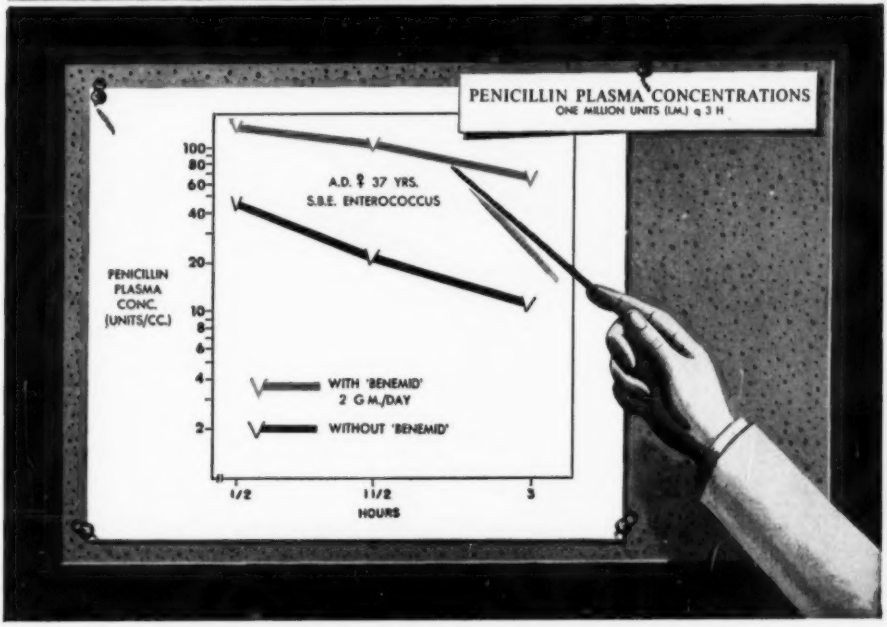
2/2270M

Remanden.

PENICILLIN WITH BENEMID®

expands the range of penicillin action

MAJOR ADVANTAGES: Supplements initial intramuscular penicillin. Given alone, produces plasma penicillin levels comparable to those of intramuscular penicillin.[1]



The 'Benemid' in REMANDEN raises plasma penicillin levels.[2]

The 'Benemid' component in REMANDEN "increases penicillemia by 2 to 10 times and infections ordinarily regarded as untreatable with penicillin have been successfully managed."[1,2] With REMANDEN most of the penicillin is recirculated without interfering with normal renal function.

The oral penicillin of choice in many common infections, REMANDEN may also be used as adjunct to parenteral therapy of fulminating infections. *Supplied: Tablets,* REMANDEN-100 and REMANDEN-250, providing 100,000 or 250,000 units of potassium penicillin G with 250 *mg.* of 'Benemid.'

NEW *Suspension* REMANDEN-100 (in 60 cc. bottles)—one tsp. equals one REMANDEN-100 tablet.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

References: 1. Antibiotics & Chemotherapy 2:555, 1952. 2. A.M.A. Exhibit, June 1951.

now

true spasmolysis

of skeletal muscle

flexin*

(Zoxazolamine†, McNeil)

the first orally effective lissive‡

Dosage: Usual children's dosage 1 tablet two to four times a day with food or immediately after meals. Children over 10 may require 2 tablets two to four times a day. FLEXIN tablets may be crushed and mixed with a suitable vehicle such as apple butter, jelly, honey or molasses.

Supplied: Yellow, scored tablets (250 mg.), bottles of 50.

†U.S. PATENT PENDING *T.M.

‡**Lissive:** Relief of skeletal muscle spasm without interference with normal function.

(1) Abraham, E. H., and Baird, H. W., III: J.A.M.A. 160:749 (Mar. 3) 1956. (2) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. 160:752 (Mar. 3) 1956. (3) Amols, W.: J.A.M.A. 160:743 (Mar. 3) 1956. (4) Smith, R. T.; Kron, K. N.; Peak, W. [illegible] and Hermann, L. F.: J.A.M.A. 160:745 (Mar. 3) 1956.

in 28 spastic children... "a decrease of muscular tone on passive flexion in every instance"[1]

Synthesized and characterized by McNeil Laboratories, "...[FLEXIN] appears to exert a somewhat selective depressing effect on subcortical and spinal polysynaptic neural pathways."[2] "Its chief advantages are oral route of administration, long duration of action, and minimal side-effects."[3]

Outstanding benefits are reported in cerebral palsy. "The administration of zoxazolamine (FLEXIN) in 28 children, each of whom had spasticity, produced a decrease of muscular tone on passive flexion in every instance."[1] In 15 of these 28 children, there was definite clinical improvement in functional abilities.

Other Disorders: Encouraging results have also been reported in a significant number of patients with spinal spasticity such as multiple sclerosis,[2] and in musculoskeletal disorders such as fibrositis, cervical root syndrome and noninflammatory rheumatoid arthritis.[4]

McNeil Laboratories, Inc. • Philadelphia 32, Pa.

McNEIL

discontinuous film lets skin function normally

PROOF

Photomicrograph of Johnson's Baby Lotion. Discontinuous film of homogeneously dispersed micron-sized droplets protects and lubricates baby skin.

- allows access of air to skin
- permits normal heat radiation
- insensible moisture escapes readily
- combats miliaria and other irritations

bettering baby care through specialized research

BABY PRODUCTS DIVISION

Johnson & Johnson

THORAZINE* *can help your patients to endure the suffering caused by severe pain*

for example: ***in burns***

Thorazine's ataraxic, tranquilizing action can reduce the suffering caused by the pain of severe burns. 'Thorazine' acts, not by eliminating the pain, but by altering the patient's reaction—enabling him to view his pain with what has been described as "serene detachment." Karp et al.,[1] reporting on the use of 'Thorazine' in patients with severe pain, observed that 'Thorazine' produced "a quiet, phlegmatic acceptance of pain."

It is obvious that not all cases of severe pain are suitable for 'Thorazine' therapy. 'Thorazine' is most useful when the psychic element is important.

'Thorazine' is available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

1. Karp, M., et al.: Am. J. Obst. & Gynec. *69*:780 (April) 1955.

Now you can be sure your patients receive full therapeutic doses of salicylates. Aspirin Supprettes rectally achieve the same salicylate blood levels as do equal oral doses, without gastric or rectal irritation.

ASPIRIN SUPPRETTES

- Ideal when oral therapy is difficult or impossible
- In febrile conditions accompanied by nausea or vomiting
- To eliminate local gastric irritation
- For prolonged salicylate therapy
- In rheumatic fever
- For relief of emotional trauma of fever, pain, insomnia

ASPIRIN w/SECOBARBITAL SODIUM SUPPRETTES

- For safe, rapid sedation of short duration
- In insomnia, anxiety states
- To quiet hyperexcitability
- Preoperatively

SUPPLIED:

Aspirin Supprettes: 1 gr., 3 gr., 5 gr. and 10 gr.
Aspirin w/Secobarbital Supprettes:
No. 1—(aspirin 1 gr., secobarbital sodium ⅛ gr.).
No. 2—(aspirin 3 gr., secobarbital sodium ¾ gr.).
No. 3—(aspirin 5 gr., secobarbital sodium ⅝ gr.).
No. 4—(aspirin 10 gr., secobarbital sodium 1¼ gr.).
IN JARS OF 12.

THE "NEOCERA" BASE MAKES THE DIFFERENCE

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent.
*Trademark U.C.C.

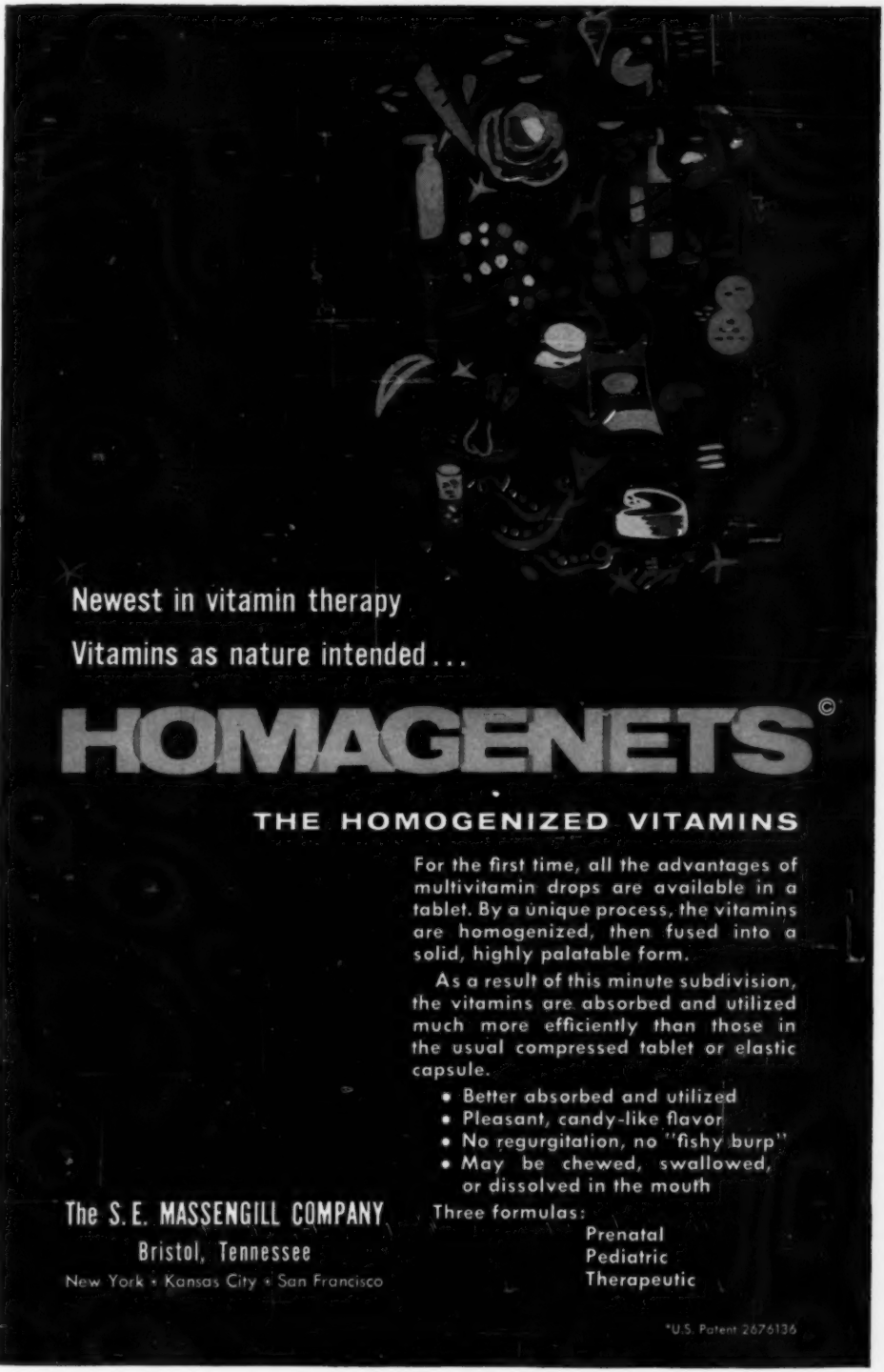
ASPIRIN SUPPRETTES and ASPIRIN w/SECOBARBITAL SODIUM SUPPRETTES

NO REFRIGERATION NECESSARY

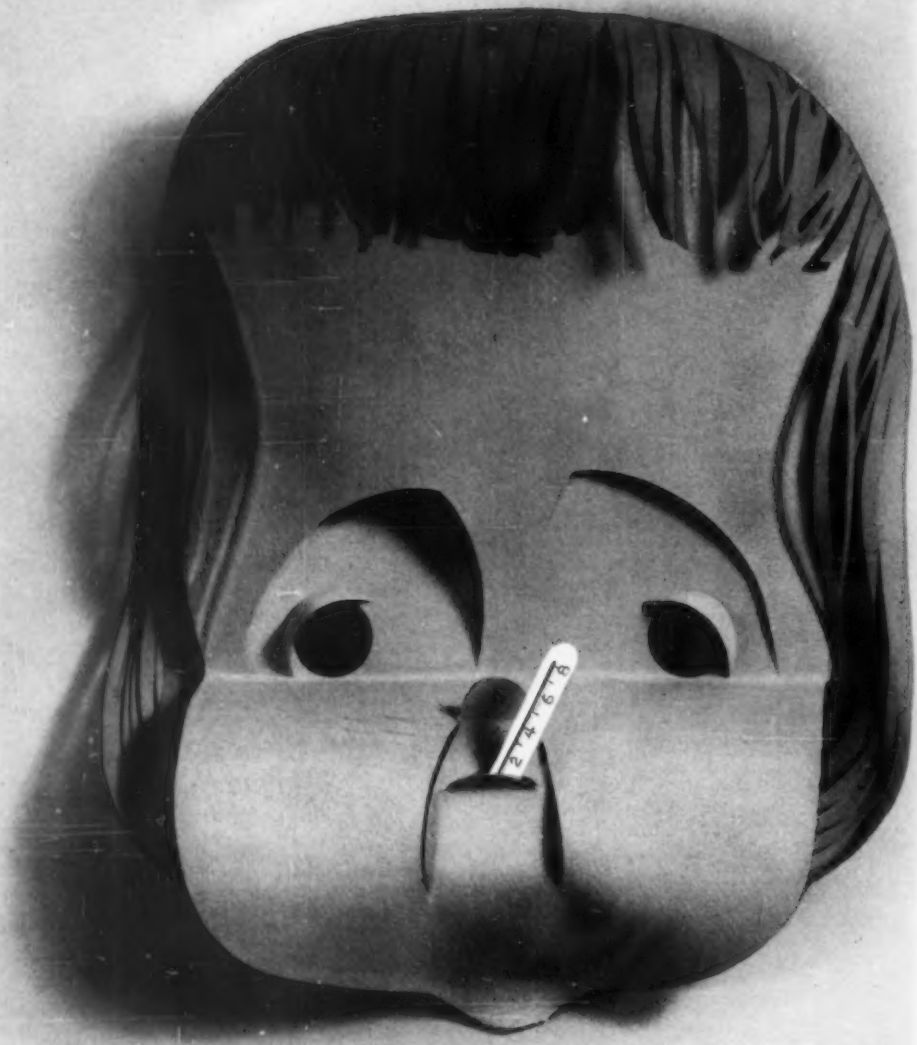
Samples on Request

Webster

THE WILLIAM A. WEBSTER COMPANY • MEMPHIS 5, TENN.


Newest in vitamin therapy
Vitamins as nature intended . . .
HOMAGENETS©
THE HOMOGENIZED VITAMINS
For the first time, all the advantages of multivitamin drops are available in a tablet. By a unique process, the vitamins are homogenized, then fused into a solid, highly palatable form.
As a result of this minute subdivision, the vitamins are absorbed and utilized much more efficiently than those in the usual compressed tablet or elastic capsule.
• Better absorbed and utilized
• Pleasant, candy-like flavor
• No regurgitation, no "fishy burp"
• May be chewed, swallowed, or dissolved in the mouth
Three formulas:
Prenatal
Pediatric
Therapeutic
The S. E. MASSENGILL COMPANY
Bristol, Tennessee
New York • Kansas City • San Francisco
*U.S. Patent 2676136

specific



few side

ctherapy

Specific—because you can actually pinpoint the therapy for coccic infections. That's because you know most bacterial respiratory infections are caused by staph-, strep- and pneumococci. *And these are the organisms most sensitive to* ERYTHROCIN —even when they resist other antibiotics.

Pediatric

Erythrocin® STEARATE

(Erythromycin Stearate, Abbott)

ORAL SUSPENSION

Low toxicity—because ERYTHROCIN (compared to many other antibiotics) rarely alters intestinal flora. *Thus, children seldom get gastroenteral side effects.* Or loss of vitamin synthesis in the intestine. Another important point—no allergic reactions. *Pediatric* ERYTHROCIN Stearate comes in a tasty, cinnamon-flavored suspension. In 75-cc., pour-lip bottles. Abbott

effects

606188

Pluralizes Potency 4 Times!

Now, 4 Clinically-Proven Sulfonamides Unite for Safe, Superior Action

Katrasul

Chimedic

By combining 4 powerful sulfas in one palatable preparation, Katrasul provides a broad-spectrum of activity 4 times as potent as any single sulfa—with toxicity reduced to practically zero.

Katrasul's quadruple formula includes Sulfadiazine, Sulfamerazine, Sulfamethazine and Sulfacetamide—individually notable for antibacterial action—in combination exerting a 4-way antibacterial spectrum of unmatched efficacy and power.

Using only fractional dosage of each sulfa results in greater solubility and the virtual elimination of crystalluria. Sensitization reactions and toxic effects approach zero.

Prescribe Katrasul to combat both gram positive and gram negative bacilli. It is effective not only against the common microorganisms, but also the gonococcus, meningococcus, pneumococcus, staphylococcus and streptococcus infections.

Delightful coconut-custard flavor invites patient- acceptance.

•

Prompt action, safety, and pleasant taste make Katrasul highly useful in the treatment of children's infectious diseases.

•

Available: Delicious coconut-custard flavored suspension. 4oz., pints, gallons. Also in tablets.

CHICAGO PHARMACAL COMPANY

5547 N. Ravenswood Ave., Chicago 40, Illinois

Pacific Coast Branch

381 Eleventh St., San Francisco, Calif.

...and adding dual control

to Meti-steroid skin therapy—

protection

against infection

new

Meti-Derm ointment

with Neomycin

enhanced effectiveness

in allergic, inflammatory

dermatoses when

minor infection

is present

or anticipated

neomycin in addition to prednisolone, free alcohol—for protective coverage against virtually all pathogenic skin bacteria with a well-tolerated, *topical* antibiotic.

formula: Each gram of water-washable METI-DERM Ointment with Neomycin contains 5 mg. (0.5%) prednisolone, and 5 mg. (0.5%) neomycin sulfate equivalent to 3.5 mg. neomycin base.

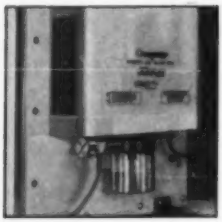
packaging: METI-DERM Ointment with Neomycin, 10 Gm. tube.

Schering

MD-J-656

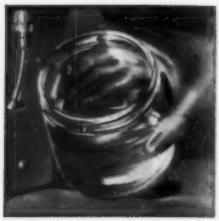
4 new features

1. New CROUPETTE pressure gauge eliminates guesswork due to defective flowmeters. To produce optimal cool vapor, simply set flow to proper sector of gauge.



2. All operating instructions are located on the CROUPETTE itself; separate, legible panels at every point concerned. No more booklets to become dirty, dog-eared or lost.

3. New, stainless steel atomizing assembly is easier to clean, more durable, and should never need to be replaced. Adaptable to all earlier CROUPETTE models as well.



4. Wide-mouth, standard glass jar simplifies filling and cleaning, provides easier access to the new, stainless steel atomizer, and may be readily replaced if broken.

of the No.1 Croup Tent:

Visibility and accessibility are CROUPETTE features. This earlier model is as efficient as the day it was first used, more than seven years ago.

No wonder the CROUPETTE® *is standard equipment* in over 3,000 hospitals and 96 per cent of U. S. medical schools. First "cool-vapor" therapy tent, the CROUPETTE has no interior obstructions; no cumbersome, high-pressure connections. Ice chamber and controls are out of reach of patient, but easily accessible to the nurse. Fresh, moisture-saturated air is effectively cooled and oxygenated by exclusive CROUPETTE recirculation. Aerosol or oxygen therapy can be easily administered. Light, compact, portable, easy to set up or to store, and with no moving parts, the new, improved CROUPETTE is as simple as it is safe and efficient. Order now, with 30-day return privilege. Phone us collect: OSborne 5-5200 (Hatboro, Pa.)

The Croupette® portable, cool-vapor therapy tent

Designed, manufactured, sold and serviced by AIR-SHIELDS, INC. *Hatboro, Pa.*

MEAD

in the critical first months of life

select the level of vitamin protection the baby needs

NEW... With stable B_{12a}

Deca-Vi-Sol

10 nutritionally significant vitamins

Each 0.6 cc. supplies	
Vitamin B_{12} (mcg.)	1
Biotin (mcg.)	30
Panthenol (mg.)	3
Pyridoxine (mg.)	1
Niacinamide (mg.)	10
Riboflavin (mg.)	1.5
Thiamine (mg.)	1
Ascorbic acid (mg.)	50
Vitamin D (units)	1000
Vitamin A (units)	5000

Poly-Vi-Sol®

6 essential vitamins

Each 0.6 cc. supplies	
Niacinamide (mg.)	6
Riboflavin (mg.)	0.8
Thiamine (mg.)	1
Ascorbic acid (mg.)	50
Vitamin D (units)	1000
Vitamin A (units)	5000

Tri-Vi-Sol®

3 basic vitamins

Each 0.6 cc. supplies	
Ascorbic acid (mg.)	50
Vitamin D (units)	1000
Vitamin A (units)	5000

Deca-Vi-Sol, Poly-Vi-Sol and Tri-Vi-Sol are

- highly stable—refrigeration not required
- readily accepted—exceptionally pleasant flavor, no unpleasant aftertaste

Full dosage assured—can be dropped directly into baby's mouth. Supplied in 15 cc., 30 cc. and economical 50 cc. bottles.

Plastic 'Safti-Dropper' —calibrated, unbreakable—supplied with each bottle.

MEAD | SYMBOL OF SERVICE IN MEDICINE

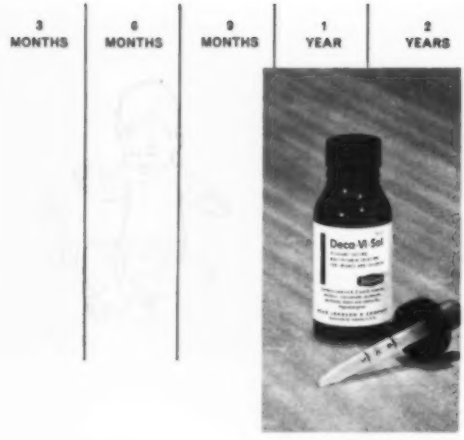
MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

for the vital first decade...

it's easier to specify

the 'Deca' VitaminF

10 nutritionally significant vitamins . . . A, D and C, plus 7 B vitamins, including B_6 and stable B_{12}



solution

Deca-Vi-Sol

10 nutritionally significant vitamins

Deca-Vi-Sol is a pleasant-tasting, fruit-flavored solution, affording maximal vitamin protection in dropper dosage. Highly stable, Deca-Vi-Sol requires no refrigeration. 15, 30 and economical 50 cc. bottles with the Mead unbreakable, calibrated plastic 'Safti-Dropper.'

emulsion

Deca-Mulcin

10 nutritionally significant vitamins

A delicious orange flavor and generous formulation make Deca-Mulcin the ideal vitamin emulsion for preschool children. Free-flowing and non-sticky, Deca-Mulcin is easy to give by teaspoon. Refrigeration is not required since Deca-Mulcin is highly stable. Pouring-lip bottles of 4 and 8 fl. oz.

MEAD

inFamily because

- **one basic family name–'Deca'**
- **one basic formulation**
- **one standard of truly comprehensive protection**

  Providing assured protection against vitamin inadequacies of "normal" diets during the vital first decade

- **3 convenient dosage forms, all with stable B_{12}**

capsules

Deca-Vi-Caps

10 nutritionally significant vitamins

Bright in color and small in size, Deca-Vi-Caps are readily accepted by school-agers. Generous formulation assures well-rounded vitamin protection during the years of rapid growth. Bottles of 30.

MEAD | SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

MEAD

in the management
of your food-sensitive
patients, specify

Liquid **Sobee**®

hypoallergenic soya formula | milk-free

a soybean protein food for sound nutrition

When you specify *Liquid* Sobee, the eczema and gastrointestinal disturbances caused by milk allergy are usually promptly relieved. These disturbances, when due to other food allergens, are also usually relieved by using *Liquid* Sobee as the basis of an elimination diet. *Liquid* Sobee is exceptionally well taken and well tolerated. Stools are satisfactory; diaper staining is no problem.

"Thermo-flash" sterilization gives *Liquid* Sobee a pleasant, bland flavor . . . attractive, light color . . . permits maximal preservation of amino acids and important B vitamins.

In a study reported by Kane,* babies on Sobee showed:

Satisfactory growth and nutrition . . . 99% relief of eczema, 90% relief of gastrointestinal and/or non-dermatologic symptoms . . . excellent acceptance.

*From an exhibit by Sydney H. Kane, M.D., at the American Medical Association meeting, Atlantic City, N. J., June 6-10, 1955.

MEAD | SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

when full formula feedings seem desirable in diarrheas...

Liberal oral feeding rather than oral food restriction in infant diarrhea is being increasingly practiced as a result of recent clinical observations and studies. Good results with full formula feedings have been reported by Chung (cited by Holt[1,2] and Nelson[3]). Parenteral electrolyte and fluid replacement was given as needed, initially and throughout treatment.

No deleterious effects of the full feeding regimen were noted, Nelson[3] states in his discussion of Chung's studies. The course of the disease was apparently not prolonged. Though fecal loss of nutrients increased, absorption of nitrogen, fat, sodium, potassium, calcium and chloride improved. As Holt[1] comments: "Increasing the concentration of nutrients in the intestinal lumen seems to promote the passage of these nutrients through the intestinal epithelium and increases their absorption."

(1) Holt, L. E., Jr.: Quart. Rev. Pediat. 9: 1, 1954. (2) Holt, L. E., Jr., and McIntosh, R.: Holt Pediatrics, ed. 12, New York, Appleton-Century-Crofts, Inc., 1953, p. 250. (3) Nelson, W. E., in Nelson: Textbook of Pediatrics, ed. 6, Philadelphia, W. B. Saunders Co., 1954, pp. 757-765.

Probana

What it is: Probana is a uniform blend of Powdered Protein Milk (Mead) 50%, casein hydrolysate 10%, banana powder 20%, and dextrose 20%.

The Probana formula was developed in collaboration with Dorothy Andersen, M.D., who, with other investigators, had used various combinations of nutrients in pancreatic fibrosis and other celiac syndromes. Probana has proved valuable in marasmus and steatorrhea due to various causes, and in other conditions which cause intolerance of usual formulas.

A formula supplying 20 calories per fluid ounce is easily prepared with 1 packed level measure of Probana and 2 ounces of water

Probana is supplied in 1 pound cans, with special measure enclosed.

as part of the regimen in infant diarrheas

specify

Probana®

Therapeutic Infant formula

provides sound nutrition... well tolerated

Probana supplies protein, fats and sugars in forms which infants with digestive and metabolic handicaps can easily utilize. It is frequently well tolerated where other formulas cannot be taken.

MEAD

SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY EVANSVILLE 21, INDIANA, U.S.A.

Dilute formulas
in newborn period

Today, mothers and babies go home from the hospital much earlier than they did a few years ago. Consequently, formula and feeding instructions for the newborn period assume greater importance.

"The first formula feedings should be relatively dilute," as pointed out by Lee in a recent text,* "and the earliest consideration should be aimed at supplying adequate fluid." Overfeeding in the newborn period "is to be avoided since it frequently leads to digestive disturbances, colic and dietary diarrhea." When the formula is made safely dilute, "most infants can be allowed to take as much of it as they desire to satisfy their hunger."

Lee recommends the feeding of dilute formulas for the first 10 to 20 days of life.

*Lee, H. F., in Lull & Kimbrough: Clinical Obstetrics, Philadelphia, Lippincott, 1953, pp. 630-632.

Dilute feedings for the newborn period are conveniently prepared with *Liquid* Lactum.

For a formula supplying 10 calories per fluid ounce: use 1 part *Liquid* Lactum with 3 parts water.

For a formula supplying 13 calories per fluid ounce: use 1 part *Liquid* Lactum with 2 parts water.

For a formula supplying 16 calories per fluid ounce: use 1 part *Liquid* Lactum with 1½ parts water.

•

For babies allergic to milk...

Liquid SOBEE® provides a good-tasting *soya formula* that is exceptionally well taken and well tolerated, relieves both gastrointestinal disturbances and eczema, and promotes sturdy growth.

the Mead formula
for general use
in infant feeding

LIQUID Lactum®

ready-prepared milk and Dextri-Maltose® formula

When you prescribe *Liquid* Lactum, you provide all the nutritional safeguards of a milk and carbohydrate formula in well balanced proportions —plus the convenience appreciated by modern mothers.

Lactum is the only infant formula that offers all these advantages: authoritative formulation • generous protein • spaced carbohydrate absorption • whole milk nutrients • optimal digestibility • maximum convenience

Let Mead products and services help you in the varied phases of infant feeding

MEAD | SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

Designed FOR THE MOST DELICATE SKIN OF ALL...

DERMOLATE®

A remarkably mild, lathering skin detergent in cake form. It cleanses completely and is gentle for use on soap-irritable or acutely inflamed skin.
Dermolate is unsurpassed for routine daily bathing of infants and children.
...4 oz. cakes...

ACIDOLATE®

A bland, non-lathering cleanser in *liquid form,* that removes fat-soluble and water-soluble skin soil with equal efficiency. Acidolate is especially useful in pediatrics to dissolve oils and ointments on the skin and hair or for the removal of scales, crusts, "cradle cap" and vernix caseosa.
...bottles of 8 fl. oz. and 1 gal....

WHITE LABORATORIES, INC., Kenilworth, N. J.

DOXINATE*

A Better Answer to the Problem of Constipation

Permits normal bowel habits—"... [Doxinate] certainly seems to be a better answer to this problem [constipation] than do any of the therapeutic agents previously available."[1]

Effective—"In all patients, the administration of dioctyl sodium sulfosuccinate proved to be an effective fecal softener."[2]

Gradual action—"The softening effect of ... [Doxinate] on the stool was apparent on the average in 48 hours."[1]

Nontoxic—"dioctyl sodium sulfosuccinate has wide usefulness in ... constipation ... without the danger of toxicity or decreasing effectiveness ..."[3]

Doxinate acts **only** on the bowel **content.**

Doxinate increases the wetting ability of intestinal fluids as much as 25 times. The resulting homogenization of fecal material makes the stool soft and yet well-formed for easy evacuation.

Doxinate is completely free of irritant laxative or "bulk" effect—nor is flatulence or oily leakage ever a problem.

Doxinate does not cause bowel movement. Instead, it **permits** normal bowel habits.

dosage:

Adults: one green 60 mg. capsule daily or one to three orange 20 mg. capsules daily.

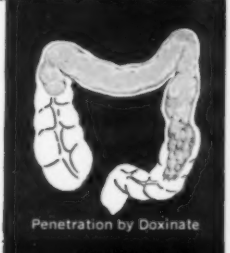
Infants and children: 1 cc. or 2 cc. once daily in formula, milk or orange juice.

1. Spiesman, M. C., and Malow, L.: Journal-Lancet (June) 1956.
2. Antos, R. J.: Southwestern Med. *37*:236 (April) 1956.
3. Wilson, J. L., and Dickinson, D. G.: J.A.M.A. *158*:261 (May 28) 1955.

Permits normal bowel habits

Effective

Gradual action



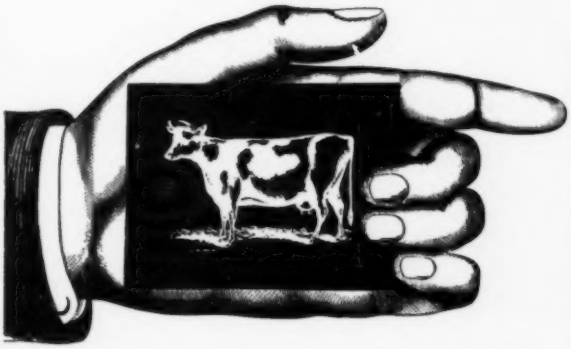
Nontoxic

DOXINATE*

The original dioctyl sodium sulfosuccinate for constipation

LLOYD
Brothers, Inc.
Cincinnati 3,
Ohio
*Patent Pending

We've given the cow a hand!



HI-PRO Spray Dried Modified Cow's Milk takes up where cow's milk leaves off. It gives a 3-to-1 protein-to-fat ratio to patients in need of biologically complete protein content and low fat intake.

HI-PRO provides a full quota of calories without danger of fat irritation in cases of fat intolerance or where digestive disturbances are present. Readily digestible, it is ideal in treatment of infant diarrhea, premature, fat intolerance and normal newborns.

infant diarrhea
Proteins are well-absorbed and supply calories lost by reduction in fat and carbohydrates.

premature
Rapid growth plus low fat tolerance makes HI-PRO an ideal food.

fat intolerance
Protein is well-absorbed and caloric intake can be raised to any level without fat difficulties.

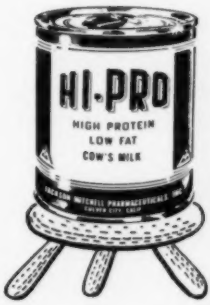
normal newborns
With HI-PRO, you can provide extra protein without fat for rapid growth and good tissue turgor.

hi-pro, analysis—dry

Protein	41%
Fat	14%
Carbohydrate	35%
Calcium	1.15%
Calories per oz.	121

For complete literature and samples write:
JACKSON-MITCHELL
Pharmaceuticals, Inc.
Culver City, California

Serving the Medical Profession Since 1934



HI-PRO is available in 1-lb. and 2½-lb. vacuum-packed tins at all pharmacies.

*VARAMEL

EASY STEPS

+ carbohydrate

+ water

*Made from Grade A Milk (U.S. Public Health Service Milk Code) which has been modified by replacement of the milk fat with animal and vegetable fats and by the addition of synthetic vitamins. No carbohydrate has been added.

THE BAKER LABORATORIES, INC.

Milk Products Exclusively for the Medical Profession

Main Office: Cleveland 3, Ohio • Plant: East Troy, Wisconsin

"Functional vomiting
should be carefully distinguished from organic vomiting. Grave consequences may follow if evidences of organic derangement . . . are masked by treatment designed to control vomiting alone."[1]

SAFE

Safety First | in emesis therapy

Prescribe

EMETROL®

(Phosphorated Carbohydrate Solution) *First*

SAFE

EMETROL will not suppress symptoms arising from organic etiology. It controls vomiting of functional origin quickly.

Dosage: Adults, 1 or 2 tablespoonfuls; infants and children, 1 or 2 teaspoonfuls, as often as every 15 minutes. Always administer *undiluted,* and forbid oral fluids for at least 15 minutes after each dose. Even if first dose is not retained, continue administration. If vomiting is not controlled within one or two hours, look for organic etiology. For individual dosage regimens in various indications, please send for literature.

1. Bradley, J. E.: Mod. Med. 20: [illegible] No. [illegible], 1952.

SAFE

Kinney **KINNEY & COMPANY, INC.** Columbus, Indiana

to restore appetite and promote weight gain

LACTOFORT®

FOR RELUCTANT FEEDERS

LACTOFORT
The Complete Pediatric Nutritive Supplement

the first pediatric dietary formulation to provide adequate quantities of L-lysine for optimal growth and for the stimulation of normal appetite—

PLUS *all* essential vitamins in excess of dietary allowances,

PLUS essential iron and calcium.

2 measures (2.3 Gm.) of Lactofort supply:

L-lysine (from L-lysine monohydrochloride)	500	mg.
Vitamin A acetate	3750	U.S.P. Units
Vitamin D	1000	U.S.P. Units
Thiamine mononitrate	0.75	mg.
Riboflavin	1.25	mg.
Niacinamide	7.5	mg.
Vitamin B_{12}	2.5	mcg.
Folic Acid	0.25	mg.
Ascorbic acid (from sodium ascorbate)	75	mg.
Pyridoxine hydrochloride	0.75	mg.
Calcium pantothenate	7.5	mg.
Iron ammonium citrate green (elemental iron 7.5 mg.)	50	mg.
Calcium gluconate (elemental calcium 130 mg.)	1.45	Gm.

Supplied: In 46 Gm. bottles with special Lactofort measuring spoon enclosed.

WHITE LABORATORIES, INC., **Kenilworth, N. J.**

new anticolic

over 90% improvement in infant colic

PEDIATRIC PIPTAL®

relieves symptoms usually within 24-48 hours

effective: 92.6% clinical improvement in 94 colicky infants*

59.6% excellent | 33.0% good | 7.4% slight

well tolerated: 93.5% 123 infants, all except 6 less than 8 weeks old when first seen*

93.5% no significant side effects

constipation and tenesmus, 4.9%
flushing no fever, 1.6%

dosage: For colic, administer 0.5 cc. with dropper supplied, directly into mouth of infant *15 minutes before feeding, on a demand-feeding schedule.* In some severe cases, 1 cc. may be advisable. For spitting, vomiting, pylorospasm, cardiospasm and other functional gastrointestinal disorders, 0.5 to 1 cc., q.i.d., by dropper or in milk, formula or fruit juice.

supplied: 30-cc. dropper bottles, with droppers calibrated to deliver 0.5 cc. Each cc. contains 4 mg. of PIPTAL and 6 mg. of phenobarbital (warning, may be habit forming).

PIPTAL is the only brand of N-ethyl-3-piperidyl-benzilate methobromide.

*Andelman, M. B.; Nathan, L. A.; Breslow, L., and Gerber, H.: Scientific Exhibit, American Academy of Pediatrics, Chicago, Ill., Oct. 3-6, 1955.

LAKESIDE

59788

ACID MANTLE®— CREME or LOTION — DOME, pH4.2
instantly restores normal acidity to the skin which has been made alkaline by contact with urine, and thus prevents diaper rash.
AVAILABLE: Creme in 4 oz. plastic jar, Lotion in 4 oz. plastic squeeze bottle.

CORT-DOME™ MICRONIZED HYDROCORTISONE ALCOHOL in Exclusive Acid Mantle base, pH4.6.
AVAILABLE: Creme or Lotion, in ½, 1, 2 and 4 oz. sizes.

CRUDE COAL TAR—"The Most Valuable Local Remedy there is for Most Infants and Children with Atopic Dermatitis."*

KOLPIX®A and KOLPIX®D—Whole Crude Coal Tar in Exclusive Acid Mantle Base. "... the tar has been treated so that it is a medium gray color instead of black and the base is not greasy but water soluble. The strength of each is 2% tar. Kolpix 'A' is for acute, somewhat active eczema, Kolpix 'D' for chronic eruptions. Neither is very dirty. These are fine preparations – I use them a great deal."* AVAILABLE: 1 oz. tubes, 2 and 4 oz. jars.

*Lewis Webb Hill, M.D., "Treatment of Eczema in Infants and Children," Journal of Pediatrics, Vol. 47, No. 6, Dec. 1955.

DOME CHEMICALS INC.
109 W. 64th ST. NEW YORK 23, N.Y.

designed for your pediatric patient

HESPER-C LIQUID

Brings established medication for capillary fragility to pediatric patients.

Now HESPER-C LIQUID's delightful orange flavor, aroma and color will appeal to your most finicky little patient.

More doctors are thinking of capillary fragility and abnormal capillary permeability in:

The severe, extended infections peculiar to children. Children subject to frequent colds – undoubtedly, in such children, the mucous membranes have poor resistance to infection, and improvement in capillary status may have an important influence in strengthening resistance.....

Allergic and asthmatic children.....

Pre- and postoperative care.....

Children who seem to bleed readily.....

Certain eczemas.....

HESPER-C LIQUID–the original synergistic nutritional supplement for capillary integrity – provides 100 mg. of fully active hesperidin concentrate plus 100 mg. ascorbic acid per teaspoonful (5 ml.) of liquid.

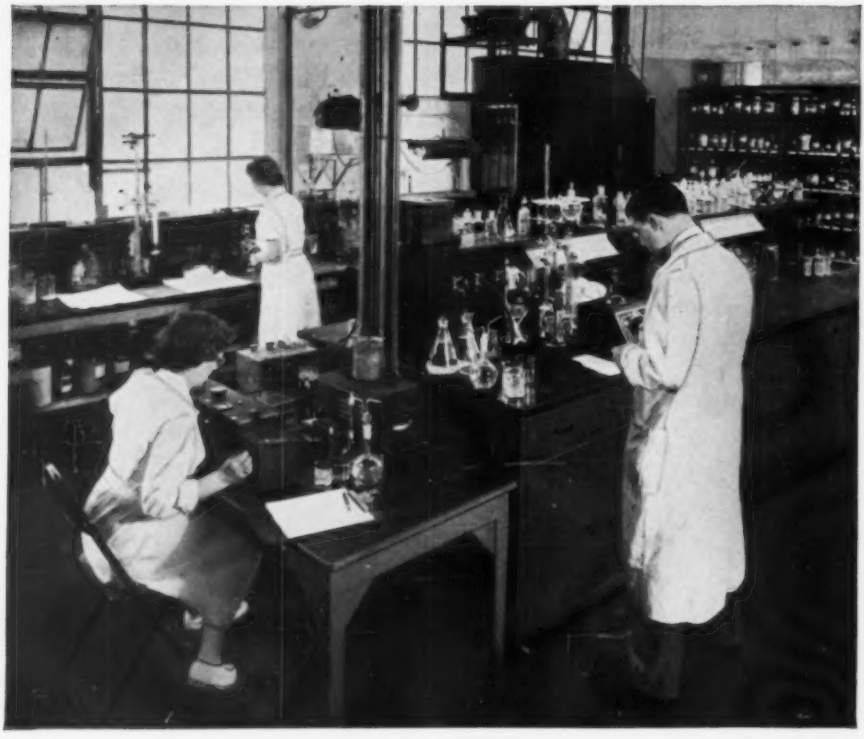
Dosage: 2 to 3 teaspoonfuls daily.

Supplied: Special 4-oz. bottle; also available in the 12-oz. size.

PRODUCTS OF ORIGINAL RESEARCH

NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL

THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.



The Beech-Nut formula for Baby Foods:

Painstaking devotion to the highest standards of quality

This formula means buying only choice fruits and carefully cultivated vegetables from select farms and orchards. They are then painstakingly cleaned and prepared by Beech-Nut experts to preserve the "just picked" freshness and fine natural flavor, with maximum retention of vitamins and minerals.

5 Pre-Cooked Baby Cereals
28 Strained Foods
27 Junior Foods

BEECH-NUT PACKING COMPANY

excellent

remedy

for a

poor

appetite

INCREMIN*

Lysine-Vitamin Drops

- combines the amino acid, l-Lysine, with vitamins B_1, B_6, B_{12}
- stimulates appetite, effects better utilization of protein, thereby promoting growth
- cherry-flavored drops are delicious; may also be mixed in milk, formula, etc.
- handy 15 cc. plastic dropper-bottle

For the problem eaters, for the underweight, for the generally below-normal child

(Excellent, too, for stimulating appetites of the elderly patient!) Dosage: 0.5 to 1 cc. (10-20 drops) daily. Each cc. (20 drops) contains:

l-Lysine	300 mg.
Vitamin B_{12}	25 mcgm.
Thiamine (B_1)	10 mg.
Pyridoxine (B_6)	5 mg.

Lederle

LEDERLE LABORATORIES DIVISION

AMERICAN CYANAMID COMPANY

PEARL RIVER, NEW YORK

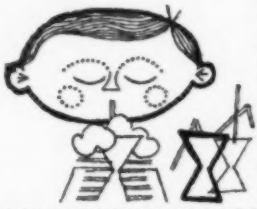
*REG. U. S. PAT. OFF.

when they
don't eat
enough

G

or won't
eat in
balance

R



here's a
new way
to help them

O

outgrow
their clothes
. . . and . . .

W

perk up
their lagging
appetites

T

delicious
melt-in-the-mouth
flavor, too

H

STIMAVITE* *for growth*

TASTITABS*

Each STIMAVITE Tastitab contains:

Vitamin B_1 . . . . . 10 mg.
Vitamin B_6 . . . . . 3 mg.
Vitamin B_{12} . . . . . 20 mcg.
Vitamin C (as Sodium Ascorbate) 25 mg.
L-lysine . . . . . 15 mg.

Dosage: One tablet daily as a dietary supplement. The tablet may be swallowed whole, allowed to melt in the mouth, or can be dissolved in fluids.

Supplied: Bottles of 30 tablets.

*Trademark

ROERIG

Chicago 11, Illinois

Upjohn

Delta-Cortef* for inflammation, neomycin for infection:

Neo-Delta-Cortef†

TOPICAL OINTMENT

Each gram contains:

Delta-1-hydrocortisone acetate 5 mg. (0.5%)

Neomycin sulfate . . . . . 5 mg.
(equiv. to 3.5 mg. neomycin base)

Methylparaben . . . . . 0.2 mg.

Butyl-p-hydroxybenzoate 1.8 mg.

Supplied: 5-gram tubes

EYE-EAR OINTMENT

Each gram contains:

Delta-1-hydrocortisone acetate 2.5 mg. (0.25%)

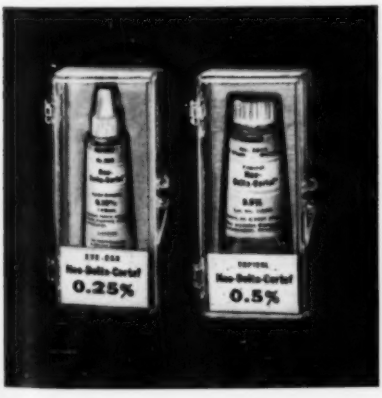
Neomycin sulfate . . . . . 5 mg.
(equiv. to 3.5 mg. neomycin base)

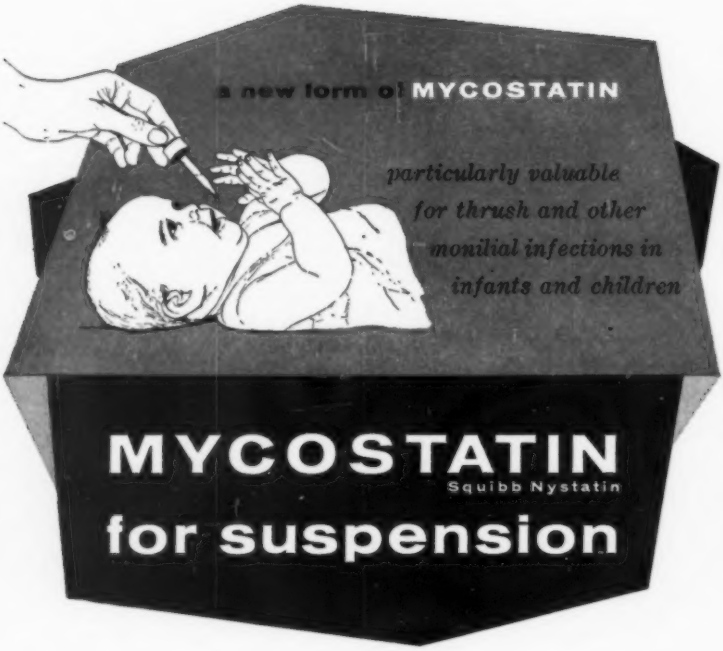
Supplied: ⅛ oz. tubes with applicator tip

*TRADEMARK

†TRADEMARK FOR THE UPJOHN BRAND OF PREDNISOLONE ACETATE WITH NEOMYCIN SULFATE

The Upjohn Company, Kalamazoo, Michigan





The usual pediatric dosage for oral or intestinal moniliasis is 1 cc. dropped into the mouth four times daily.

When reconstituted by the pharmacist in 22 cc. of distilled water, each cc. of the suspension contains 100,000 units of the antifungal antibiotic, nystatin. 24-dose bottles, with dropper calibrated at 1 cc.

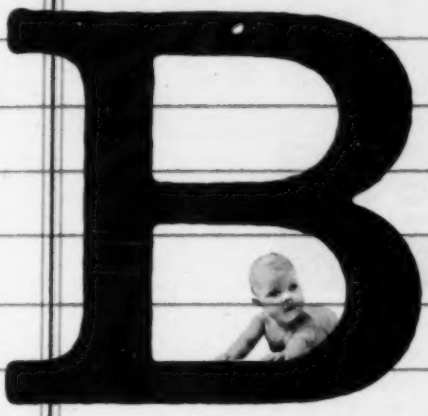
also available:

MYCOSTATIN Vaginal Tablets (100,000 units): packages of 15.
MYCOSTATIN Ointment (100,000 units per gram): 1-ounce tubes.
MYCOSTATIN Oral Tablets (500,000 units): bottles of 12 and 100.

Squibb Quality—the Priceless Ingredient

SQUIBB

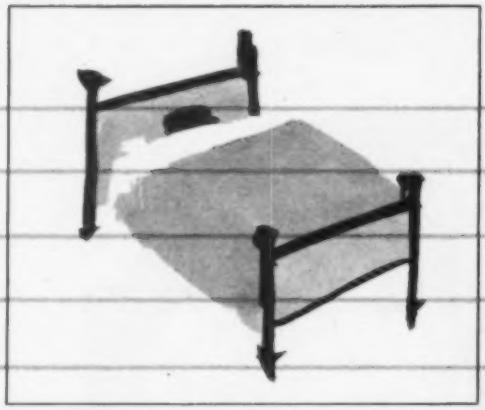
"MYCOSTATIN"® IS A SQUIBB TRADEMARK



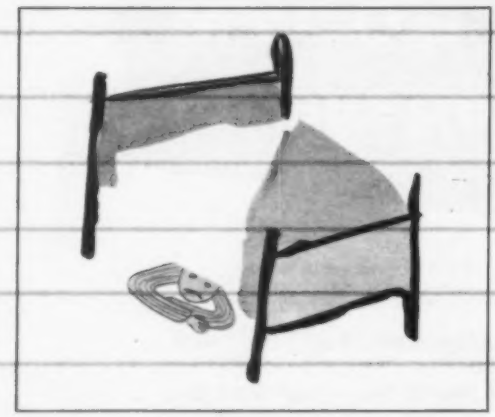
is for...
B certain

You can be certain of adequacy in essential B factors (including "anticonvulsive" B_6) when you specify Vi-Penta® Drops for your newborn patients. Every bottle is dated to assure full potency. Twenty drops (0.6 cc) given daily provide a full complement of eight essential vitamins.

ROCHE



Against infections



Against objections

Gantrisin® (acetyl) Pediatric Suspension is effective against a wide range of bacterial infections, and its appealing raspberry flavor overcomes objections to taste and tablet medication. Well tolerated ... no alkalies needed.

Hoffmann - La Roche Inc · Nutley · N.J.

ROCHE

Helps fill nutritional needs of a cross section of your patients

PEDIATRIC • ADOLESCENT • GERIATRIC

Cerofort®

elixir

(Critically essential L-lysine with important B vitamins)

Efficient tissue synthesis requires

- all the essential amino acids
- simultaneously
- in the correct proportions,[1] e.g., as in animal proteins.

Synthesis lags when lysine is low

An average of 20 to 40 per cent of dietary protein consists of cereal or wheat protein which is likely to be 50 per cent lysine deficient. Numerous authorities report that, "By adding a small quantity of lysine, the over-all amino acid balance is corrected and tissue building value approximately doubled."[2]

Daily dose of 3 teaspoonfuls, one with each meal, provides:

L-Lysine Monohydrochloride	790 mg.*
Vitamin B_{12}	25 mcg.
Thiamine Hydrochloride	10 mg.
Riboflavin	10 mg.
Pyridoxine Hydrochloride	2 mg.
Niacinamide	100 mg.
Panthenol	20 mg.

Alcohol 5%

*Equivalent to 600 mg. L-lysine

Supplied in bottles of 8 fl. oz.

REFERENCES

1. Cannon, P. R.: J.A.M.A. *135*:1043, 1947.
2. Flodin, N. W.: American Miller & Processor *81*:30, 1953.

and to help fill the nutritional gap between sickness and health in major illness, injury, or surgery:

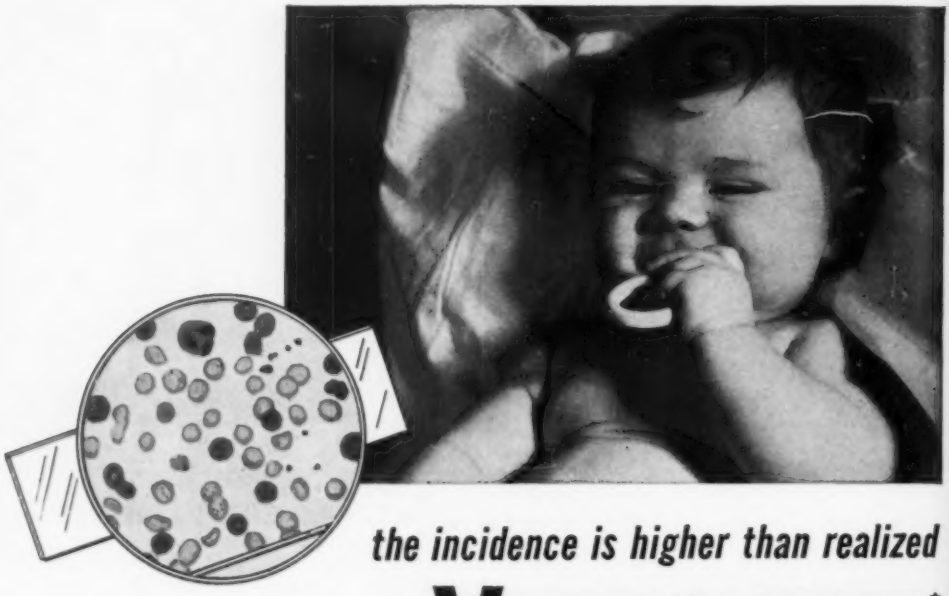
Cerofort tablets

(L-lysine plus all the important vitamins)

first with lysine

White's WHITE LABORATORIES, INC., Kenilworth, New Jersey

Heavy Metal Poisoning



the incidence is higher than realized

Calcium Disodium **VERSENATE***

spells the answer

At last, here is a dependably effective means of removing heavy metals from the body *without danger of organ damage.* Calcium Disodium VERSENATE is now available for oral as well as intravenous therapy; the intravenous form for safe, effective, dramatic short-term treatment; the oral form for convenient prevention of exacerbations or as sole therapy for milder types of lead poisoning.

NOW IN 2 DOSAGE FORMS

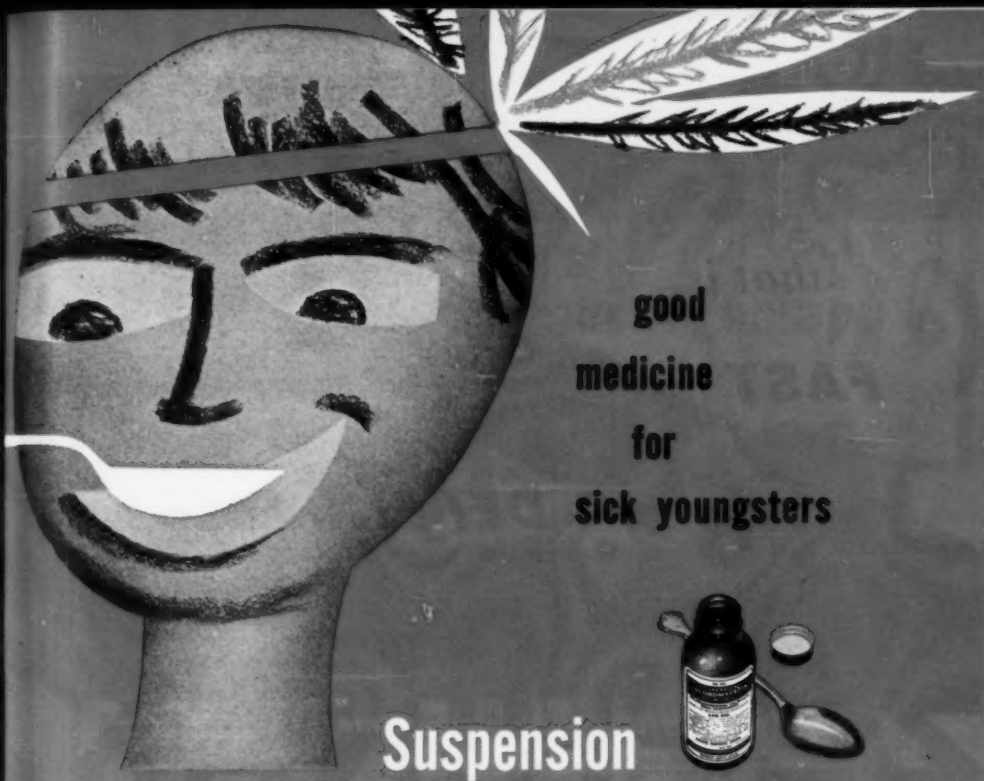
INTRAVENOUS Complete instructions for dilution and administration accompany the ampuls. The average daily dose for children is not more than 0.5 Gm. per 35 pounds of body weight, given once or twice daily. (Adult dose, 1 to 2 Gm. per day, given as two infusions.) In boxes of six 5 cc. (1 Gm.) ampuls.

ORAL For children, the dose is adjusted on the basis of 2 tablets (1 Gm.) per 35 pounds of body weight daily, in divided doses. For ease of administration tablets may be crushed and dissolved in milk. (Average adult dose is 8 tablets (4 Gm.) per day, in divided doses.) In bottles of 250 tablets, each containing 500 mg.

Write for descriptive booklet

*Trademark of Dow Chemical Co.

Riker LOS ANGELES



good
medicine
for
sick youngsters

Suspension Chloromycetin® Palmitate

pleasant-tasting Chloromycetin for pediatric use

Your young patients won't hit the war path at medication time when the prescription calls f SUSPENSION CHLOROMYCETIN PALMITATE. Its appealing custard flavor rates it as "good me icine" with the most rebellious braves.

Good medicine, too, for a wide variety of infections in infancy and childhood, CHLOROMYCET (chloramphenicol, Parke-Davis) affords rapid recovery and speedy convalescence.

Because of its liquid form, dosage of SUSPENSION CHLOROMYCETIN PALMITATE is easily adjuste That it needs no refrigeration is an additional convenience to every harassed mother.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been as ciated with its administration, it should not be used indiscriminately or for minor infections. Furth more, as with certain other drugs, adequate blood studies should be made when the patient requi prolonged or intermittent therapy.

supplied: SUSPENSION CHLOROMYCETIN PALMITATE, containing the equivalent of 125 mg. Chloromycetin in each of 4 cc., is available in 60-cc. vials.

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

Antisepsis

that is

FAST

and

DEPENDABLE!

ZEPHIRAN

chloride

–brand of refined benzalkonium chloride–is an antiseptic that is

fast – kills many gram-positive and gram-negative bacteria in seconds.

dependable – reliable bactericidal and bacteriostatic effectiveness combined with marked wetting and penetrating activity.

well tolerated – virtually nontoxic and nonirritating to tissue cells – well tolerated in surface application or irrigation.

versatile – for antisepsis in surgery, obstetrics and gynecology; urology; dermatology; eye, ear, nose and throat; pediatrics and general practice. Excellent for instruments, too!*

economical – 1 oz. Zephiran concentrate makes 1 gallon of 1:1000 Zephiran solution.

*with Anti-Rust Tablets (Winthrop)

Zephiran® chloride scores every time!

Zephiran chloride TINCTURE 1:1000
tinted and stainless
bottles of 8 fl. oz. and 1 gallon
Zephiran chloride AQUEOUS SOLUTION 1:1000
bottles of 8 fl. oz. and 1 gallon
Zephiran chloride CONCENTRATE 12.8%
aqueous solution (must be diluted
– 1 oz. makes 1 gallon of 1:1000
solution), bottles of 4 fl. oz. and 1 gallon

Winthrop LABORATORIES

New York 18, N. Y. • Windsor, Ont.

Zephiran, trademark reg. U. S. Pat. Off. 1954 M

in diaper rash

99% success reported for this means of therapy!

effective... A series of 500 cases of diaper dermatitis[1] was treated—with cure resulting in all but three infants. Wherever erythematous, intertriginous zones developed in the diaper region accompanied by the pungent odor of ammonia, treatment was instituted. Ammoniacal odor disappeared with gradual relief of symptoms. As a control, 50 healthy, normal infants were given prophylactic treatment. None developed ammonia dermatitis. PEDAMETH promises effective therapy!

safe... dl-Methionine is safe since it is actually one of the nutritionally essential amino acids. New and Non-Official Remedies (1952) states, "Because Methionine is low in toxicity, its use is not likely to be attended by any untoward effects". Goldstein[1] states that "untoward effects were conspicuously absent". PEDAMETH promises safe therapy!

convenient... Simply open a capsule and add the contents to the baby's daily formula, preferably while it is still warm. Or if preferred, it may be given in fruit juice or water. But no matter how it is given—PEDAMETH is convenient therapy!

1. Goldstein, Louis S., Clinical Medicine 59:455 (1952).

Each capsule contains 0.2 Gm. of dl-Methionine.

prescribe

"PEDAMETH"

(dl-methionine

S·F·DURST & COMPANY, Inc., Philadelphia 20 Pa.

Send for samples and literature

Child Life SHOES

made to merit your professional recommendation

100% Genuine Goodyear Welt Construction
Longer-Wearing Genuine Cordovan Sole
Specially Shaped, Tempered Spring Steel Shank
Thomas Heel Arch Extension
Inner Wedged Thomas Heel
Ankle Embracer Heel Fit
Quarter Overlap — No ripped back seams

CHILD LIFE "Arch Feature" shoes are so constructed with "built-in" features that certain foot deficiencies can be corrected without need for further wedging. These shoes are also excellently suited for additional modification, as you may prescribe.

A. Supple leather counter molded to embrace and support ankle

B. Broad toe area for full freedom of action

C. Ample width at the insole for the ball of the foot

D. 100% Goodyear Welt Construction

CHILD LIFE "Regulars" are shoes you can recommend with utmost confidence when mothers ask about footwear for their children. In outline above, you see the "specification data" of CHILD LIFE lasts. These shoes also lend themselves well for your prescription work.

In almost every community from coast-to-coast, you'll find a qualified and franchised CHILD LIFE shoe dealer. These men and women have been selected for their knowledge of good fitting practices, and for their specific interest in children's footwear. You'll find them most co-operative and attentive to your prescription work. Please write for full information on CHILD LIFE shoes — on the market since 1924 — and the names of the CHILD LIFE dealers nearest you.

HERBST Shoe Manufacturing Company

Milwaukee 45, Wis.

new tar-steroid therapy

for sub-acute

and chronic dermatoses

TARCORTIN*

CREAM

synergistic combination
effective in resistant
and refractory cases

Tarcortin contains coal tar extract and hydrocortisone, producing—

"A more rapid and more pronounced" clinical response than would be expected "from either medication alone."[1]

This synergistic effect brings prompt relief in atopic dermatitis, nummular eczema, dermatitis venenata, anogenital pruritus, seborrhea, and other chronic and resistant dermatoses . . . improvement is often noted within one week.

Recurrent episodes of various dermatoses "which became, eventually, refractory to hydrocortisone when used alone, occurred less frequently and did not become refractory to therapy" when the steroid was combined with an agent such as tar.[2]

available: 7 gram and 1 ounce tubes.

formula: 0.5% hydrocortisone; 5% special coal tar extract (Tarbonis®)—greaseless, stainless hydrophilic vanishing cream base.

Apply twice daily to affected areas, and massage gently into skin until cream vanishes. No protective dressing is required.

R&C

REED & CARNRICK

JERSEY CITY 6, NEW JERSEY

1. Bleiberg, J.: Hydrocortisone-tar extract cream in chronic and sub-acute dermatoses, to be published.
2. Welsh, A.L., and Ede, M.: Hydrocortisone ointments: their rational use in dermatology, Ohio State M.J. *50*:837 (Sept.) 1954.

*Trademark and Pat. Appl.

"*My* child gained faster at that stage . . ."

The physician's function is complicated by the belief of many mothers that "heaviness" is the all-important indicator of physical progress. Obviously, it "cannot be taken as the *only* criterion of health and may be misleading at times. . . ."[1] More important than weight gain, per se, is *physiologic* weight gain.

This was demonstrated in a recent study of the effects of feeding breast milk and various formulas to premature infants, where high ash levels associated with high protein formulas were believed to cause ash retention, with resultant obligate water retention. Kagan and his associates[2] considered that there was a difference in the character of the increased weight gain due to high ash levels. ". . . the authors concluded that weight gain in itself is not a good index of progress."[3]

Assure physiologic weight gain with regular SIMILAC® feedings

When breast feeding isn't feasible, Similac assures physiologic nutrition by providing more calories per unit of ash. Because it closely resembles mother's milk in composition, nutritional balance and digestibility, Similac helps to reduce complications in the first year of life.

SIMILAC®

There is no closer equivalent to the milk of healthy, well-nourished mothers

REFERENCES:

1. Holt, L. E., Jr., and McIntosh, R.: Pediatrics, ed. 12, New York, Appleton-Century-Crofts, Inc., 1953, p. 12.
2. Kagan, B. M.; Hess, J. H.; Lundsen, E.; Shafer, K.; Parker, J. B., and Stigall, C.: Pediatrics *15*:373 (April) 1955.
3. Editorial: J. A. M. A. *159*:116 (Sept. 10) 1955.

ROSS LABORATORIES COLUMBUS 16, OHIO
FORMERLY M&R LABORATORIES

in rheumatoid arthritis

continuing benefits

for successful corticosteroid therapy

METICORTELONE*

(PREDNISOLONE)

- therapy usually undisturbed by sodium retention, edema, weight gain
- excellent relief of arthritic pain, swelling, tenderness
- spares patients salt-poor diets
- up to 5 times as potent as hydrocortisone

Available as 1, 2.5, and 5 mg. tablets.

METICORTELONE,* brand of prednisolone. *T.M. ML-J-66-256

Schering

most active
topical steroid

MAJOR ADVANTAGE: Weight for weight, the most effective anti-inflammatory agent yet developed for topical use.

Alflorone®

ACETATE

(FLUDROCORTISONE ACETATE, MERCK)

"... the use of fluorohydrocortisone locally for the treatment of eczema has been attended by a degree of response about 10 times greater than the unhalogenated steroid and there has been little if any adverse reaction as a result of systemic absorption."[1] Lotion is available for weeping lesions, ointment for dry lesions.

SUPPLIED: 'Alflorone' Acetate Topical Lotions—0.1% and 0.25%, 15-cc. plastic squeeze bottles. 'Alflorone' Acetate Topical Ointments—0.1% and 0.25%, 5-Gm. and 15-Gm. tubes.

1. Editorial, *Pediatrics* 16:677, November, 1955.

SHARP & DOHME

Philadelphia 1, Pa.

DIVISION OF MERCK & CO., INC.

for sustained therapeutic sulfonamide blood levels

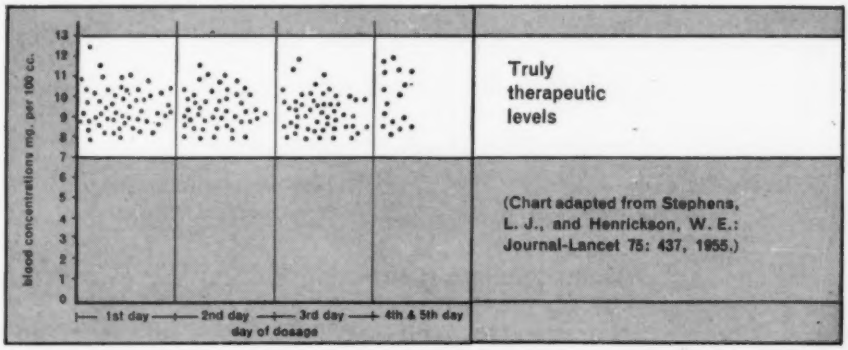
8 a.m. only twice-a-day dosage 8 p.m.

a dose here ---------- and a dose here

Lipo-Triazine*

brand of meth-dia-mer sulfonamides

HERE IS THE PROOF!



Lipo-Triazine given at 8 a.m. and 8 p.m. Blood sulfa levels determined on 1st day 8 hours after initial dose; thereafter, just a few minutes before subsequent dose. Therapeutic response uniformly good.

and you get

- better patient cooperation
- better dosage control
- greater relative safety

also available...

Lipo-Diazine*

brand of sulfadiazine

Bottles of 4 and 16 oz.

"... patients receiving Lipo-Triazine, both prophylactically and therapeutically for a variety of conditions, responded uniformly favorably to twice daily dosage at 12 hour intervals."[1]

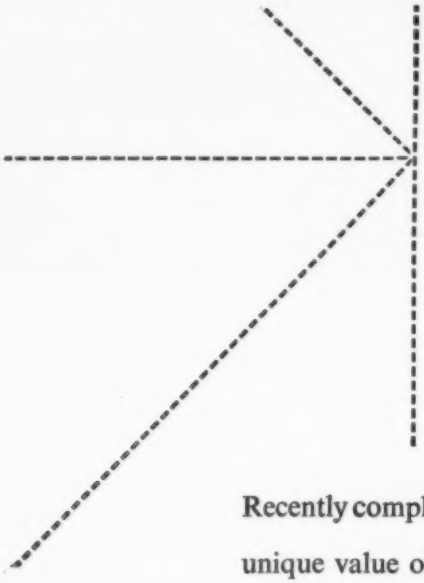
1. Stephens, L. J., and Henrickson, W. E.: Journal-Lancet 75: 437, 1955.

DONLEY-EVANS & COMPANY • ST. LOUIS 15, MISSOURI

the originators of liquid sulfas

*Exclusive trademarks of Donley-Evans & Co.; subjects of patents pending

Areas of Clinical Study / One of a series



ANEMIA OF INFANCY

Recently completed—1954—studies [1, 2] again confirm the unique value of Roncovite (cobalt-iron) in the prevention and treatment of infant anemia.

Clinical results show that routine administration of Roncovite can completely prevent the iron deficiency which so frequently develops in the first six months of life.

RONCOVITE (*Cobalt-Iron*) *has introduced a wholly new concept in anti-anemia therapy. It is based upon the unique hemopoietic stimulation produced only by cobalt. The application of this new concept has led to marked, often dramatic, advances in the successful treatment of many of the anemias.*

SUPPLIED:

RONCOVITE DROPS

Each 0.6 cc. (10 drops) provides:

Cobalt chloride.....40 mg.
(Cobalt 9.9 mg.)

Ferrous sulfate.....75 mg.

DOSAGE:

In children one year or older 0.6 cc. (10 drops); infants less than one year 0.3 cc. (5 drops); once daily diluted with water, milk, fruit or vegetable juice.

EFFECTIVE

"It is a significant fact that none of the... cases receiving iron as well as cobalt required additional iron therapy and that the haemoglobin levels of this group remained consistently and significantly higher than those in any other group after the age of 4 months."[1]

"...there can be no doubt that the average hemoglobin values... are greater in the cobalt-iron (Roncovite) treated group."[2]

PATIENT SATISFACTION

"...the mothers of these anaemic infants frequently stated spontaneously that the children were much improved, with increased appetite and vigour. It seems possible, therefore, that even if anaemia in premature infants does not usually produce marked symptoms, there is a subclinical debility which becomes more evident in retrospect."[1]

SAFETY

"There was no evidence of toxicity in any case under treatment:...There is nothing to suggest that cobalt in any way impairs the general progress or rate of weight gain in premature infants in the dosage employed."[1]

"The babies were closely observed daily for ill effects of the medication while at the premature unit and when they returned for check ups. None of them showed harmful effects despite the large doses...A few of the babies ...have been followed for more than 100 days with no ill effects noted."[2]

1. Coles, B. L., and James, U.: Arch. of Disease in Childhood *29:*85 (1954). Coles, B. L., and James. U.: Journal-Lancet *75:*79 (March) 1955. Coles, B. L.: Arch. Disease in Childhood *30:*121 (April) 1955.
2. Quilligan J. J., Jr.: Texas State J. Med. *50:*294 (May) 1954.

Bibliography of 192 references available on request.

RONCOVITE

The original, clinically proved cobalt-iron product.

LLOYD

BROTHERS, INC.

Cincinnati, Ohio

In the Service of Medicine Since 1870

Meat...

and Protein Allowances for Children

Concerned with growth as well as maintenance of tissues, protein needs of children—per pound of body weight and according to age—are one to three times as great as those of adults. These greater needs are set forth in the table of daily protein allowances recommended by the Food and Nutrition Board of the National Research Council,[1] shown below.

Since they deal with the biologic value of proteins and with the vulnerability of children to inadequate protein intake, the following statements accompanying the Board's recent announcement of protein allowances merit attention:

> "The nutritive value of proteins is primarily dependent on the amino acid composition, and the lower biological value of vegetable proteins as compared with animal proteins is well known. The inclusion of a variety of foods, and especially products of animal origin, in the diet assures a satisfactory amino acid distribution as well as sources of other nutrients . . . Recent wide-spread interest in protein deficiency syndromes such as Kwashiorkor disease[2] emphasizes the particular vulnerability of children who receive diets in which the protein content is low and primarily of vegetable origin, even when the total calorie intake is adequate or high."[1]

Meat, when cooked, presents approximately 25 to 30 per cent of high quality protein, easily digested and readily assimilable. Meat is especially acceptable to children and should be a regular item of their diets.[3] It also provides valuable amounts of B vitamins and essential minerals.

Recommended Daily Protein Allowances[1]

Children	*Protein*	Boys	*Protein*
1-3 yrs., 27 lb., 34 in.	40 Gm.	10-12 yrs., 78 lb., 57 in.	70 Gm.
4-6 yrs., 40 lb., 43 in.	50 Gm.	13-15 yrs., 108 lb., 64 in.	85 Gm.
7-9 yrs., 59 lb., 51 in.	60 Gm.	16-20 yrs., 139 lb., 69 in.	100 Gm.
		Men	
Girls		25-65 yrs., 143 lb., 67 in.	65 Gm.
10-12 yrs., 79 lb., 57 in.	70 Gm.		
13-15 yrs., 108 lb., 63 in.	80 Gm.	**Women**	
16-20 yrs., 120 lb., 64 in.	75 Gm.	25-65 yrs., 121 lb., 62 in.	55 Gm.

1. Recommended Dietary Allowances, Report of the Food and Nutrition Board, National Academy of Sciences—National Research Council, Publication 302, Washington, D.C., 1953.
2. Brock, J. F., and Autret, M.: Kwashiorkor in Africa, Bull. World Health Organ. *5*:1 (1952).
3. McLester, J. S., and Darby, W. T.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, p. 218.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago . . . Members Throughout the United States

September 25. Second and third degree burns caused by flaming gasoline. Gauze pressure dressings of White's Vitamin A & D Ointment were changed at weekly intervals.

October 25. Healing is complete with minimal scar tissue and no contractures.

SEVERE BURN OR MINOR IRRITATIONS

WHITE'S VITAMIN A & D OINTMENT

Topical application of White's Vitamin A & D Ointment speeds restoration of epithelial and connective tissues. Even severe burns respond favorably to the healing action of Vitamin A & D Ointment.

Diaper rash, chafing and abrasions also readily yield to its therapeutic and protective qualities. Prepared in suitable lanolin-petrolatum base, White's Vitamin A & D Ointment is pleasant to use, free from excessive oiliness, and will keep indefinitely. Does not stain the skin and is easily laundered from diapers or clothing.

You can prescribe it in 1½ oz. or 4 oz. tubes; 1 lb. or 5 lb. jars.

- diaper rash
- soft tissue injuries
- dry skin
- bedsores
- slow healing wounds
- varicose and diabetic ulcers
- fissured nipples

White's WHITE LABORATORIES, INC., KENILWORTH, N. J.

August 25. A typical case of diaper rash, characterized by excoriation and soreness.

September 1. After only one week of local applications with White's Vitamin A & D Ointment each time diaper was changed, the skin surface is normal.

"Afterglow" painted by Norman Rockwell to show baby's happy response to a Swift meat meal

Swift's new smoother meats are easy to enjoy...easy to digest!

As a doctor and an authority on child psychology, you understand the close affinity between baby's *enjoyment* of food and healthy growth. That happy state called "well-being" embraces them both.

Just as you do, Swift takes a vital interest in the well-being of the babies under your care. That's why we make Meats for Babies the very best you can recommend.

Nutritionally sound, these fine 100% meats are rich in the elements that contribute to good health. Wonderful-tasting and creamy-smooth, Swift's Meats also provide the mealtime pleasure that's so important to baby's well being.

All eight varieties—and Swift's Egg Yolks—are prepared with the particular care that makes them worthy of your confidence.

MEATS FOR BABIES

Swift's most precious product

IN TREATMENT OF PINWORMS

break the reinfestation cycle rectally

GENTIAN-EV

SUPPRETTES®

SUCCESSOR TO THE SUPPOSITORY

97% CURES

Within 14-28 days, virtually a 100% cure of pinworms can be obtained with combined oral medication and Gentian-Ev Supprettes rectally.[1]

NEW
TWO-PHASE ATTACK

RECTALLY—Gentian-Ev Supprettes
- Break reinfestation cycle
- Kill gravid females in rectal region
- Arrest perianal itching, scratching

ORALLY—Oxyuricidal Medication
- Destroys young and adult oxyuricides in intestinal tract

THE "NEOCERA" BASE

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent.

*Trademark U.C.C.

1. Allen, F. P., Jr.: J. Ped. 48: 155, 1955.

Composition: Each Gentian-Ev Supprette contains gentian violet 0.25% and benzocaine 2.0%, in "Neocera" dispersal base.

Supplied: In jars of 14 (one complete treatment).

NO REFRIGERATION NECESSARY
Samples on Request

GENTIAN-EV SUPPRETTES

RECTAL MANAGEMENT OF ENTEROBIUS VERMICULARIS

Webster **THE WILLIAM A. WEBSTER COMPANY, MEMPHIS 5, TENNESSEE**

portrait of a contented baby

fibrefree HYPOALLERGENIC FORMULA

1. *An ideal food for milk allergies, eczema and problem feeding*
2. *An excellent formula for regular infant feeding*

Strikingly similar to mother's milk in composition and ease of assimilation, babies thrive on SOYALAC.

Clinical data furnish evidence of SOYALAC'S value in promoting growth and development.

Protein of high biologic value is obtained from the soybean by an exclusive process.

SOYALAC is an ideal "regular" formula. It also helps solve the feeding problems of prematures and infants requiring milk-free diets.

No mixing problem with SOYALAC Concentrated Liquid. Simply dilute with equal amount of water.

FREE BOOKLET AND SAMPLES

A request on your professional letterhead or prescription form will bring complete information and a supply of samples. Address Loma Linda Food Company, Arlington, California or Mount Vernon, Ohio.

LOMA LINDA FOOD COMPANY | *Medical Products Division*

ARLINGTON, CALIF. MOUNT VERNON, OHIO

new!

SPECIFIC FOR "CRADLE CAP"

Softens and separates the scales from the scalp.

Restores normal physiologic function of the scalp epithelium and glands.

CRADOL
WITH DIAPARENE CHLORIDE
DIRECTIONS: To guard against "cradle cap" (crusts and scales on scalp), and scalp infection, gently massage CRADOL into infant's scalp 3 times a week. To relieve "cradle cap": gently massage CRADOL into scalp 3 times daily. At the end of 7 days, shampoo with mild soap and use a fine comb or scalp brush. Apply CRADOL daily to help prevent recurrence.
CONTAINS: Di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride in a suitable emulsified base.
FOUR FLUID OUNCES
BENSON-NÜEN LABORATORIES, INC. DISTR.
NEW YORK 10
TORONTO 10

another first by the makers of Diaparene® Chloride.

Cradol contains natural oils which protect the scalp against drying elements, lubricates the scalp and prevents recurrence of cradle cap.

Cradol prevents secondary infection. It contains Diaparene Chloride a well recognized and clinically proven antibacterial agent.

Supplied in 4 oz. bottles. Literature and samples on request

BENSON-NÜEN LABORATORIES, INC. • NEW YORK 10, N. Y. • TORONTO 10, CANADA
A Subsidiary of Homemakers' Products Corporation

HELPFUL HINTS

For Bottle-fed Babies
Prone to Constipation

Dear Doctor:

For bottle-fed babies with a tendency toward dry stools, Malt Soup Extract may be used routinely to maintain stool softness. One or two teaspoonfuls may be added to the regular 24-hour feeding.

Malt Soup Extract is gentle and safe. It is a dietary product, with physiologic stool-softening action. It is the most laxative of all the carbohydrate preparations.[1] There is no danger of habit formation.

1. Jeans, P. C., and Marriott, W. M.: Infant Nutrition. St. Louis, C. V. Mosby Co., 1947, Ed. 4, p. 364.

Stanley Olson
BORCHERDT MALT EXTRACT CO.

---

*Specially processed non-diastatic malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

Send for Samples and Literature

For HARD, DRY STOOLS OF CONSTIPATED BABIES

Borcherdt

MALT SOUP *Extract**

A gentle laxative modifier of milk. One or two tablespoonfuls in the day's formula—or in water for breast fed babies—produce a marked change in the stool.

SAVES DOCTOR'S TIME, TOO!

Fewer phone calls from anxious mothers. Malt Soup Extract is merely added to the formula. Prompt results. Easy for mother to prepare and administer. Does not upset the baby.

BORCHERDT MALT EXTRACT CO.
217 N. Wolcott Ave. • Chicago 12, Ill.

heal tender skin with Ammens.

Soft young skin is especially susceptible to irritation from chafing and moisture. In babies, heat and diaper rash are also frequent, troublesome problems.

Healing of irritated areas is readily achieved when AMMENS MEDICATED POWDER is used. Oxyquinolin and zinc oxide, blended in the powder, protect macerated crevices against bacterial invasion. Starch granules, evenly dispersed in talc, provide an absorbent coating which is soothing as well as healing.

Whenever skin is irritated—in adults as well as children—AMMENS is comforting, healing.

Ammens.
Medicated POWDER

BRISTOL-MYERS COMPANY
19 West 50 Street, New York 20, N. Y.

Distributor for Charles Ammen Co., Alexandria, La.

"Loose Stools" the most frequent problem in infancy

Arobon®

Loose stools in infancy pose a common but vexing problem for every pediatrician and every mother. Symptoms may not reach the stage of watery diarrhea, yet may lead to a wide variety of annoying side effects. Loose stools may be readily controlled by Arobon without resorting to medications or drastic changes in formula.

Simply stir into the formula...pleasant tasting Arobon is not a drug...yet it is a most effective and safe antidiarrheal agent ...no contraindications.

In specific diarrheas Arobon checks symptoms quickly, before physiologic effects become dangerous. An excellent aid when antibiotics are called for.

Arobon is derived from specially processed carob flour high in naturally occurring lignin, hemicellulose and pectin. It provides 2.7 calories per gram.

Composition	Per cent
Lignin, hemicellulose, pectin	22.0
Starch	15.0
Crude fiber	3.0
Soluble carbohydrates	50.5
Protein	3.5
Fat	0.5
Minerals	2.0
Moisture	3.5

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—A time-honored name in the field of infant nutrition

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References: 1. Youngblood, V. H.: J. Urol. 70:926, 1955. 2. Carroll, G.: Pediat. Clin. N. America, 1955, pp. 781-791.

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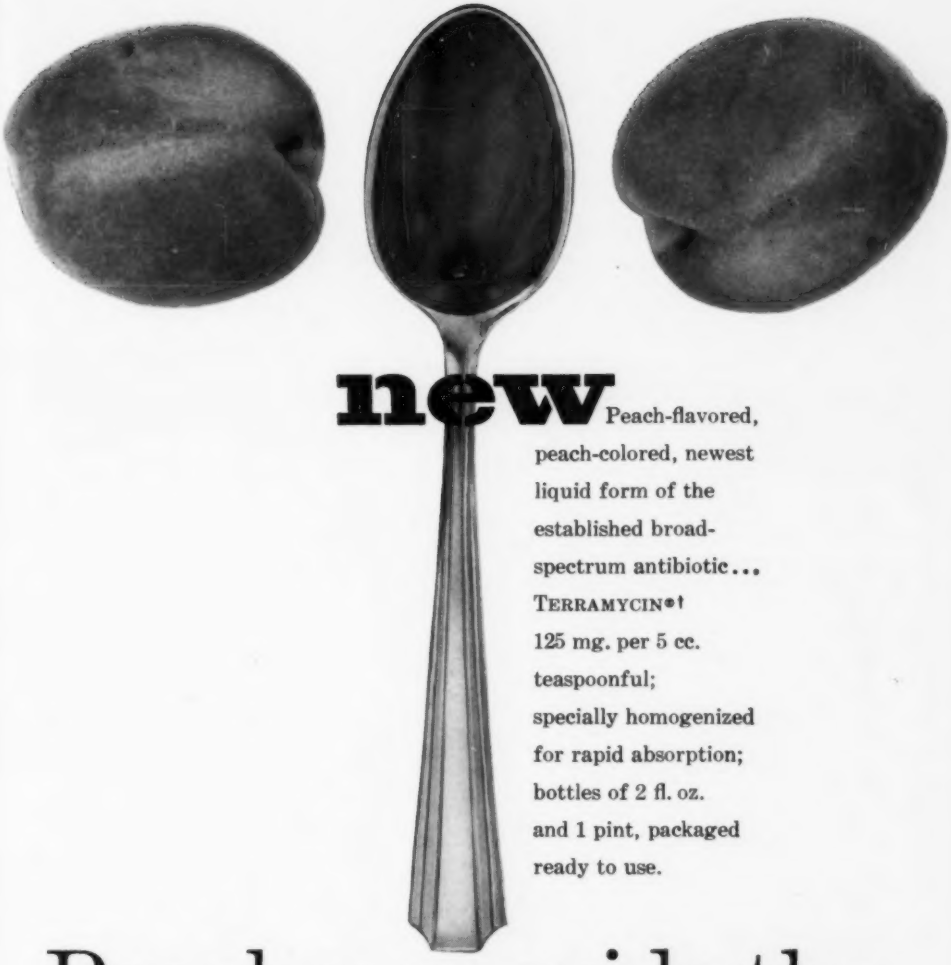

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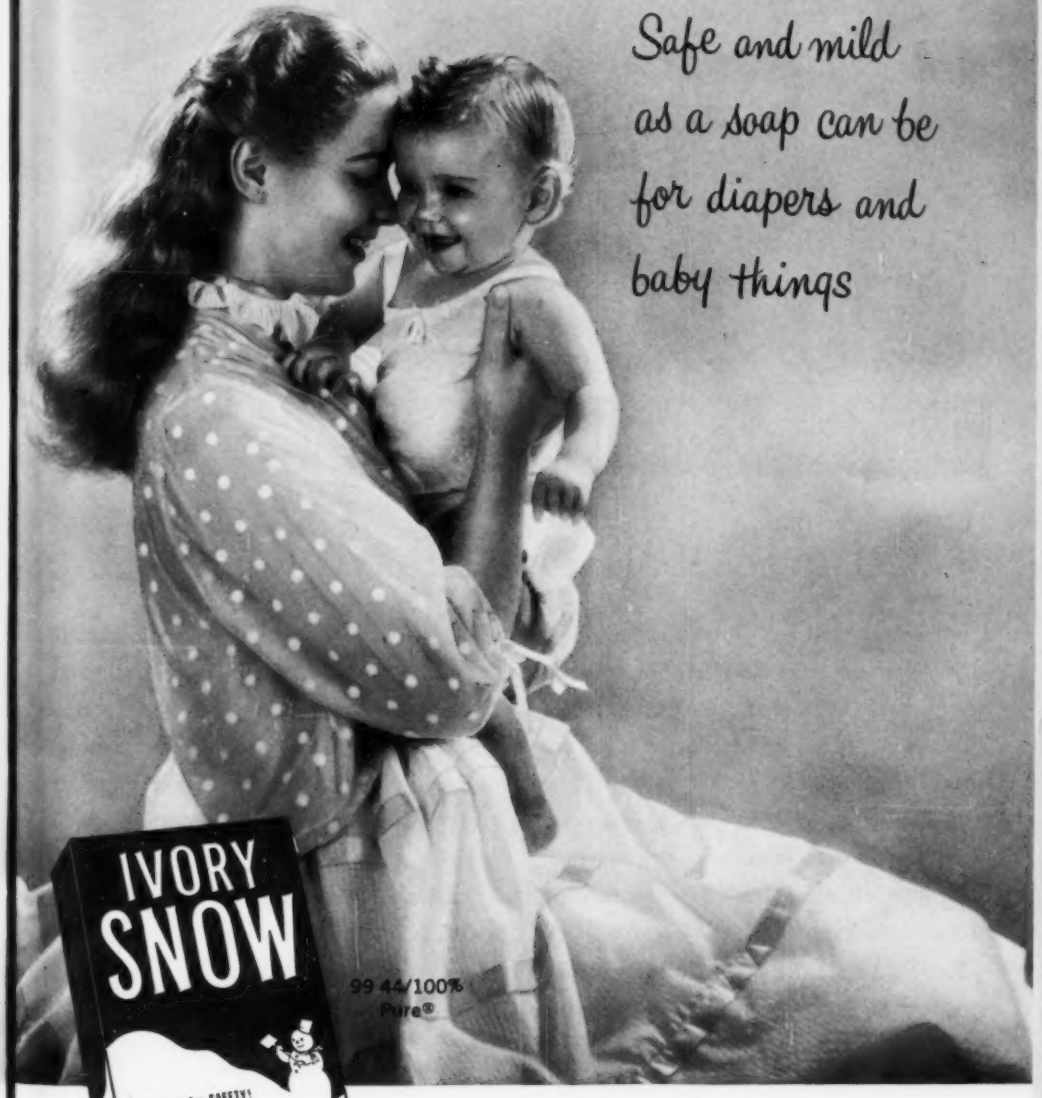
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1. Martin, E. A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, p. 141.
2. The Addition of Specific Nutrients to Foods, Public Health Reports *69*:275 (Mar.) 1954.
   Kelly, H. T.: Impact of Modern Nutrition on Twentieth Century Morbidity, Pennsylvania M.J. *58*:481 (May) 1955.
3. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 5, Philadelphia, W. B. Saunders Company, 1955, pp. 139, 140.
4. Sherman, H. C.: Food Products, ed. 4, New York, The Macmillan Company, 1948, pp. 221, 222.

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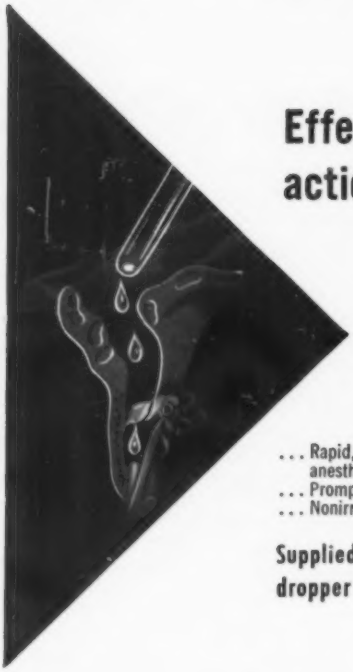

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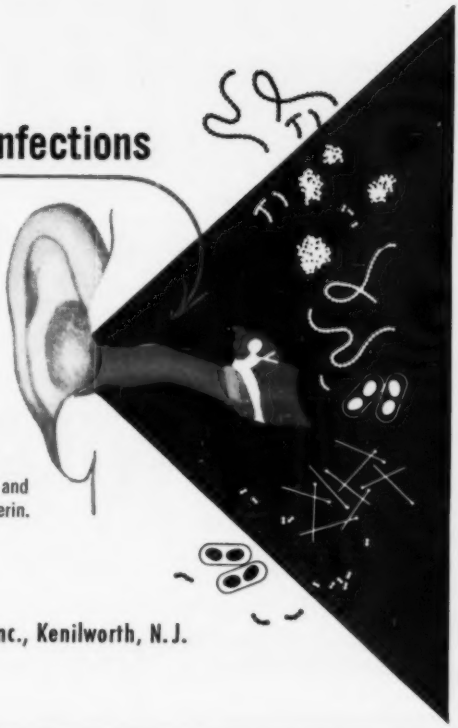

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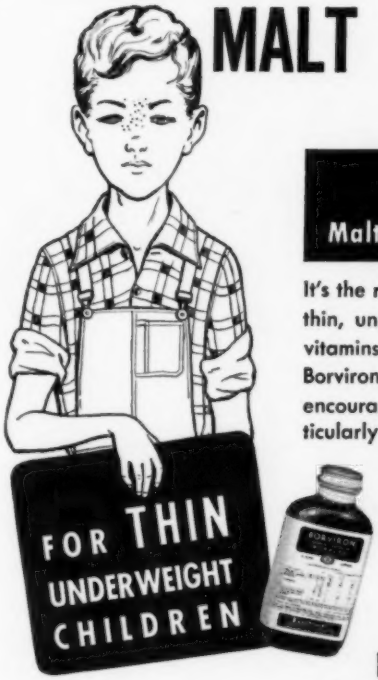

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ST. LOUIS 3, MO., U. S. A.

Entered at the Post Office at St. Louis, Mo., as Second Class Matter.

Published Monthly. Subscriptions may begin at any time.

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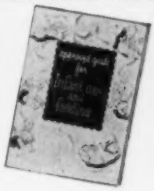

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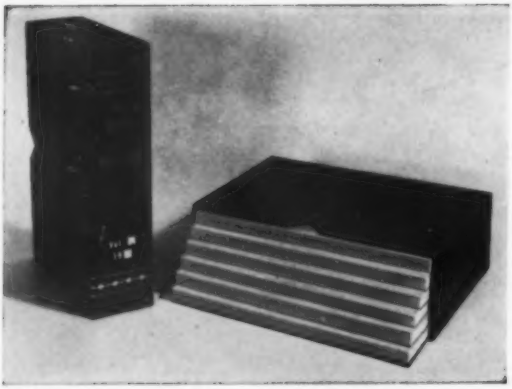

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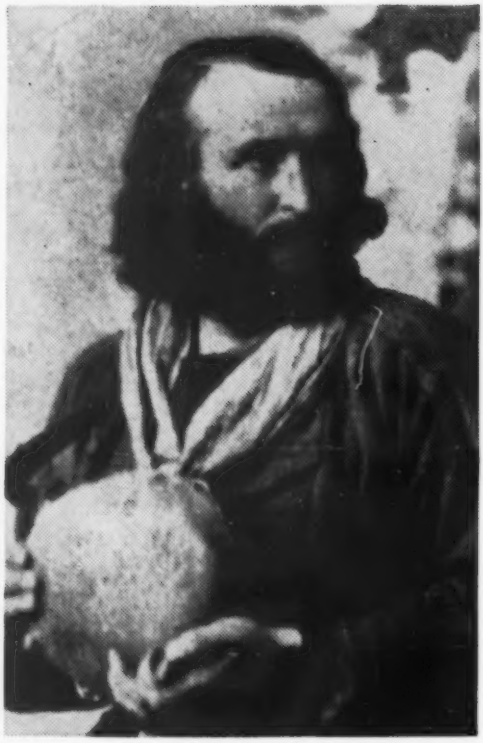

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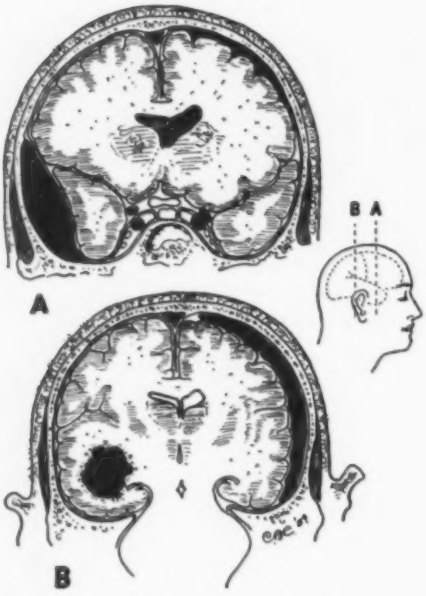

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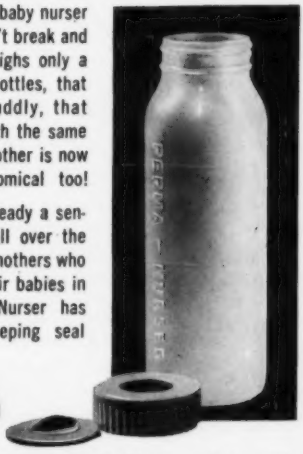

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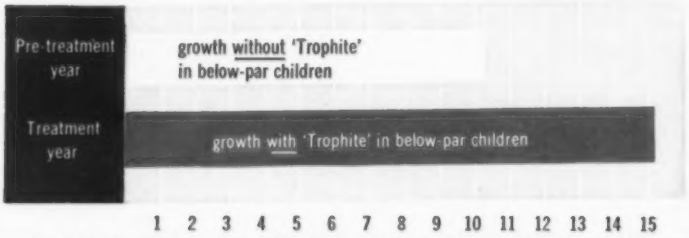
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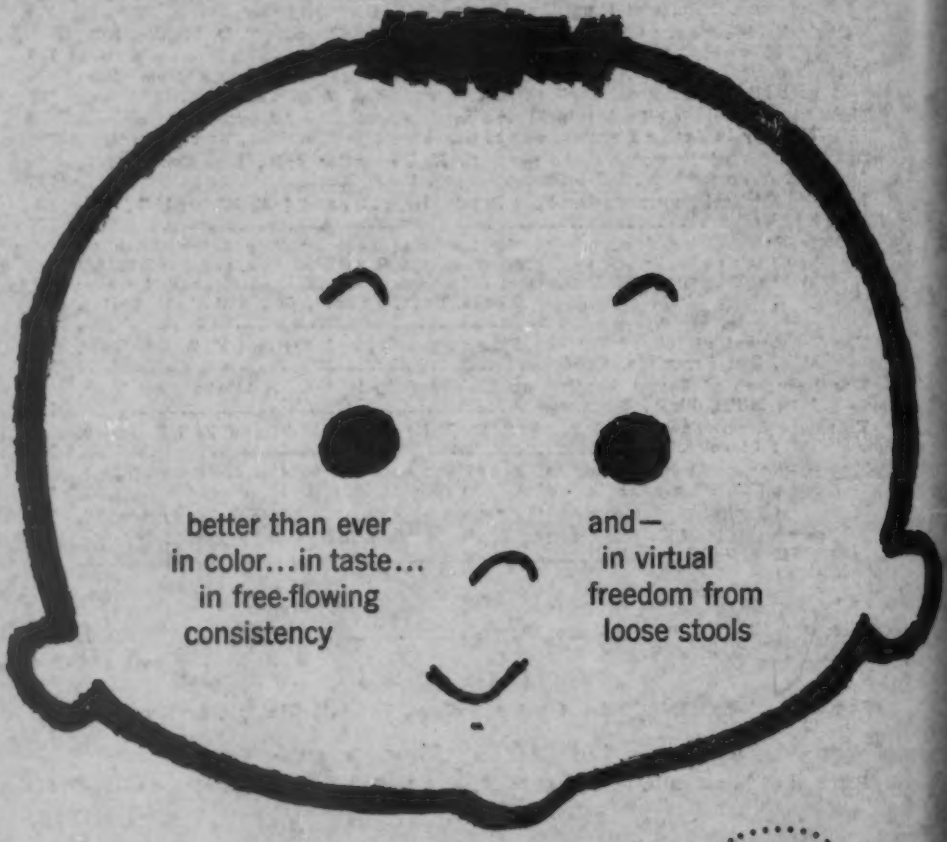

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